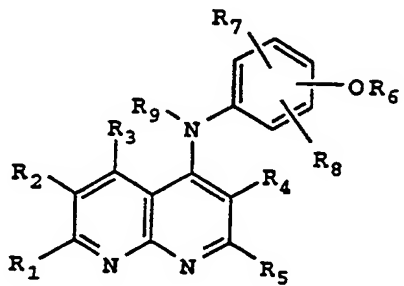




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>C07D 471/04, A61K 31/435</b> <b>// (C07D 471/04, 221:00, 221:00)</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 93/13097</b> <b>(43) International Publication Date:</b> 8 July 1993 (08.07.93)
<b>(21) International Application Number:</b> PCT/EP92/02901 <b>(22) International Filing Date:</b> 12 December 1992 (12.12.92)  <b>(30) Priority data:</b> 9127252.6 23 December 1991 (23.12.91) GB  <b>(71) Applicant (for all designated States except US):</b> THE BOOTS COMPANY PLC [GB/GB]; 1 Thane Road West, Nottingham NG2 3AA (GB).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> ARMITAGE, Bernard, John [GB/GB]; BOWEN, John, Gareth [GB/GB]; CROSSLEY, Malcolm, John [GB/GB]; HUNNEYBALL, Ian, Michael [GB/GB]; LESLIE, Bruce, William [GB/GB]; MILLER, Thomas, Kerr [GB/GB]; SPOWAGE, Michael [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB).		<b>(74) Agent:</b> THACKER, Michael, Anthony; The Boots Company plc, Patents Department, R4 Pennyfoot Street, Nottingham NG2 3AA (GB).  <b>(81) Designated States:</b> AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, RO, RU, SD, SE, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> ANTI-RHEUMATIC NAPHTHYRIDINE DERIVATIVES  <div style="text-align: center;">  </div> <div style="text-align: right;">(I)</div> <b>(57) Abstract</b> <p>This invention relates to compounds of formula (I) and pharmaceutically acceptable salts thereof in which R<sub>1</sub> represents hydrogen, alkyl, hydroxy, carboxyalkenyl, alkoxy-carbonylalkenyl, hydroxyalkyl, carboxyalkyl, alkoxy-carbonylalkyl, alkoxy, halogenated alkyl, carboxy, alkoxy-carbonyl or alkanoylamino; R<sub>2</sub> represents hydrogen, halo, alkoxy, hydroxy, alkanoyloxy, or phenoxy; R<sub>3</sub> represents hydrogen or alkyl; R<sub>4</sub> represents hydrogen, halo, alkoxy-carbonyl, a benzyloxycarbonyl, alkanoyl, benzoyl, carbamoyl, alkyl, carboxy, hydroxyalkyl or alkylthio; R<sub>5</sub> represents hydrogen or alkyl; R<sub>6</sub> represents hydrogen, alkyl [optionally substituted by one or more of the following: hydroxy, halo or an amino group of formula-NR<sub>12</sub>R<sub>13</sub>], a C<sub>3-12</sub> alicyclic hydrocarbon group, phenyl, (cycloalkyl)alkyl or benzyl; R<sub>7</sub> represents hydrogen, halo, trifluoromethyl, trifluoromethoxy, alkyl, carboxy, or alkoxy; R<sub>8</sub> represents hydrogen, halo, trifluoromethyl, trifluoromethoxy, alkyl or alkoxy; and R<sub>9</sub> represents hydrogen or alkyl; which are antirheumatic agents. Compositions containing these compounds and processes to make them are also disclosed.</p>		

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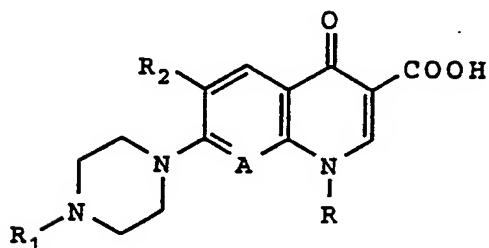
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## Anti-rheumatic naphthyridine derivatives

The present invention relates to therapeutic agents, and in particular to substituted 4(5)-amino-1,8-naphthyridines, to processes for their preparation, to pharmaceutical compositions containing them and to their therapeutic activity as anti-rheumatic agents.

Rheumatoid arthritis is currently treated with anti-inflammatory agents, which alleviate the symptoms but do not affect the progression of the condition, or with disease-modifying antirheumatic drugs e.g. gold compounds, D-penicillamine, sulphasalazine, azathioprine and methotrexate. However, most disease-modifying antirheumatic drugs are associated with side-effects, often of a serious nature. This means that such drugs are often only used as a last resort in the most serious cases. Consequently a need exists for a less toxic, disease-modifying, antirheumatic drug which may be administered orally.

EP 0,361,177 discloses compounds of formula A



A

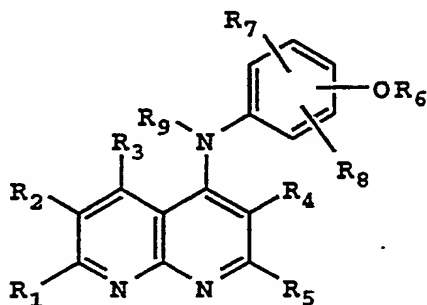
in which R represents alkyl, cyclopropyl, methylamino and p-fluorophenyl; R<sub>1</sub> represents hydrogen or a C<sub>1-2</sub> alkyl group; R<sub>2</sub> represents halo and A represents -CH- or a nitrogen atom. It is disclosed that these compounds may be used to treat rheumatoid arthritis by intra-articular administration.

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Japanese patent application number 38774/69, publication number J47-29519 (1972) discloses ethyl 4-anilino-7-methyl-1,8-naphthyridine-3-carboxylate amongst a number of compounds which are prepared as intermediates for use in the preparation of anti-bacterial agents. It is suggested that these intermediates possess anti-bacterial and antiprotozoal activity but no results are given.

2-Diethylaminomethyl-4-(7'-methyl-1',8'-naphthyridin-4'-ylamino)phenol and 2-diethylaminomethyl-4-(1',8'-naphthyridin-4-ylamino)phenol are disclosed in the Australian Journal of Chemistry, 1984, 37, 1065 as having minimal anti-malarial activity.

The present invention relates to compounds of formula I



I

and pharmaceutically acceptable salts thereof in which R<sub>1</sub> represents hydrogen, a C<sub>1-6</sub> alkyl group, hydroxy, a carboxy C<sub>2-4</sub> alkenyl group, a C<sub>2-6</sub> alkoxy carbonyl C<sub>2-4</sub> alkenyl group, a hydroxy C<sub>1-6</sub> alkyl group, a carboxy C<sub>1-4</sub> alkyl group, a C<sub>2-6</sub> alkoxy carbonyl C<sub>1-4</sub> alkyl group, a C<sub>1-6</sub> alkoxy group, a halogenated C<sub>1-6</sub> alkyl group, a carboxy group, a C<sub>2-6</sub> alkoxy carbonyl group or a C<sub>1-6</sub> alkanoylamino group;

R<sub>2</sub> represents hydrogen, halo, a C<sub>1-6</sub> alkoxy group, hydroxy, a C<sub>1-6</sub> alkanoyloxy group, or a phenoxy group

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(which may be optionally substituted by a C<sub>1-4</sub> alkyl group, halo or a C<sub>1-4</sub> alkoxy group);

R<sub>3</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group;

R<sub>4</sub> represents hydrogen, halo, a C<sub>2-7</sub> alkoxy carbonyl group, a benzyloxycarbonyl group (which may be optionally substituted by a C<sub>1-4</sub> alkyl group, halo or a C<sub>1-4</sub> alkoxy group), a C<sub>1-6</sub> alkanoyl group, a benzoyl group (which may be optionally substituted by a C<sub>1-4</sub> alkyl group, halo or a C<sub>1-4</sub> alkoxy group), carbamoyl, a C<sub>1-6</sub> alkyl group, a carboxy group, a C<sub>1-6</sub> hydroxyalkyl group or a C<sub>1-6</sub> alkylthio group;

R<sub>5</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group;

R<sub>6</sub> represents hydrogen, a C<sub>1-6</sub> alkyl group [optionally substituted by one or more of the following: hydroxy, halo or an amino group of formula-NR<sub>12</sub>R<sub>13</sub> (in which R<sub>12</sub> and R<sub>13</sub> independently represent hydrogen or a C<sub>1-4</sub> alkyl group or R<sub>12</sub> and R<sub>13</sub> together with the nitrogen atom to which they are attached represent a pyrrolidine ring, a morpholine ring or a piperidine ring)], a C<sub>3-12</sub> alicyclic hydrocarbon group, a phenyl group (which may be optionally substituted by a C<sub>1-4</sub> alkyl group, halo or a C<sub>1-4</sub> alkoxy group), a C<sub>3-6</sub> cycloalkyl C<sub>1-4</sub> alkyl group or a benzyl group (which may be optionally substituted by a C<sub>1-4</sub> alkyl group, halo or a C<sub>1-4</sub> alkoxy group);

R<sub>7</sub> represents hydrogen, halo, trifluoromethyl, trifluoromethoxy, a C<sub>1-6</sub> alkyl group, a carboxy group, or a C<sub>1-6</sub> alkoxy group;

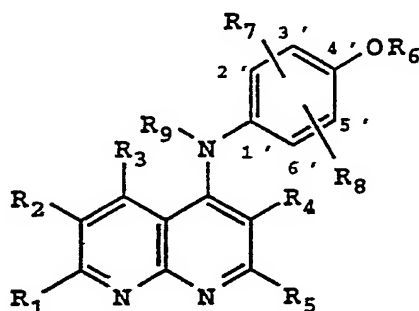
R<sub>8</sub> represents hydrogen, halo, trifluoromethyl, trifluoromethoxy, a C<sub>1-6</sub> alkyl group or a C<sub>1-6</sub> alkoxy group; and

R<sub>9</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group.

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It will be understood that a group containing a chain of 3 or more carbon atoms may be straight or branched, for example, propyl includes n-propyl and isopropyl and butyl includes n-butyl, sec-butyl, isobutyl and tert-butyl. Alicyclic groups may be bridged.

A preferred group of compounds of formula I, is represented by formula II



II

and pharmaceutically acceptable salts thereof in which

10  $R_1$  represents hydrogen, a  $C_{1-4}$  alkyl group (for example methyl, ethyl, propyl or butyl), hydroxy, a carboxy  $C_{2-4}$  alkenyl group, a  $C_{2-6}$  alkoxy carbonyl vinyl group (for example methoxycarbonyl vinyl, ethoxycarbonyl vinyl or propoxycarbonyl vinyl), an  $\omega$ -hydroxy  $C_{1-4}$  alkyl group

15 (for example hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl), a carboxy  $C_{1-4}$  alkyl group (for example carboxymethyl, carboxyethyl or carboxypropyl), a  $C_{2-6}$  alkoxy carbonyl  $C_{1-4}$  alkyl group (for example methoxycarbonylmethyl, ethoxycarbonylpropyl or

20 butoxycarbonylbutyl), a  $C_{1-6}$  alkoxy group (for example methoxy, ethoxy, propoxy or butoxy) or a polyhalogenated  $C_{1-4}$  alkyl group (for example trifluoromethyl or pentafluoroethyl);

$R_2$  represents hydrogen, halo (for example fluoro, bromo or chloro), a  $C_{1-6}$  alkoxy group (for example methoxy, ethoxy, propoxy or butoxy) or hydroxy;

25

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R<sub>3</sub> represents hydrogen;

R<sub>4</sub> represents hydrogen, halo (for example bromo or chloro), a C<sub>2-5</sub> alkoxy carbonyl group (for example methoxy carbonyl, ethoxy carbonyl, propoxy carbonyl or butoxy carbonyl), benzyloxy carbonyl, a C<sub>2-6</sub> alkanoyl group (for example acetyl, propionyl, butyryl or isobutyryl), carbamoyl, a C<sub>1-4</sub> alkyl group (for example methyl, ethyl, propyl or butyl), carboxy or an  $\alpha$ -hydroxy C<sub>1-6</sub> alkyl group (for example hydroxymethyl, 1-hydroxyethyl, 1-hydroxypropyl or 1-hydroxybutyl);

R<sub>5</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group (for example methyl, ethyl, propyl or butyl);

R<sub>6</sub> represents hydrogen, a C<sub>1-6</sub> alkyl group [optionally substituted by one or more of the following hydroxy, halo or an amino group of formula NR<sub>12</sub>R<sub>13</sub> in which R<sub>12</sub> and R<sub>13</sub> independently represent hydrogen or a C<sub>1-4</sub> alkyl group] (for example R<sub>6</sub> represents methyl, ethyl, propyl, butyl, hydroxyethyl, hydroxypropyl, dihydroxypropyl, trifluoromethyl, diethylaminoethyl), a C<sub>3-12</sub> alicyclic hydrocarbon group (for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl), phenyl or benzyl;

R<sub>7</sub> represents hydrogen, halo (for example fluoro, bromo or chloro), trifluoromethyl, a C<sub>1-4</sub> alkyl group (for example methyl, ethyl, propyl or butyl), a carboxy group or a C<sub>1-4</sub> alkoxy group (for example methoxy, ethoxy, propoxy or butoxy);

R<sub>8</sub> represents hydrogen, halo (for example fluoro, bromo or chloro), trifluoromethyl, a C<sub>1-4</sub> alkyl group (for example methyl, ethyl, propyl or butyl) or a C<sub>1-4</sub> alkoxy group (for example methoxy, ethoxy, propoxy or butoxy);

R<sub>9</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group (for example methyl, ethyl, propyl or butyl).

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In preferred compounds of formula II, R<sub>1</sub> represents hydrogen, methyl, ethoxy, trifluoromethyl, hydroxy, 2-carboxyvinyl, 2-carboxyethyl or hydroxymethyl. More preferably R<sub>1</sub> represents hydrogen, methyl, ethoxy, trifluoromethyl or hydroxy. Most preferably R<sub>1</sub> represents methyl or ethoxy.

In preferred compounds of formula II, R<sub>2</sub> represents hydrogen, methoxy, ethoxy, propoxy or bromo. More preferably R<sub>2</sub> represents hydrogen, ethoxy or bromo.  
10 Most preferably R<sub>2</sub> represents hydrogen or ethoxy.

In preferred compounds of formula II, R<sub>3</sub> represents hydrogen.

In preferred compounds of formula II, R<sub>4</sub> represents hydrogen, bromo, ethoxycarbonyl, 1-butyryl, carboxy, carbamoyl, hydroxymethyl or 1-hydroxybutyl. More preferably R<sub>4</sub> represents hydrogen, ethoxycarbonyl or 1-butyryl. Most preferably R<sub>4</sub> represents hydrogen or ethoxycarbonyl.

In preferred compounds of formula II, R<sub>5</sub> represents hydrogen or methyl. More preferably R<sub>5</sub> represents hydrogen.  
20

In preferred compounds of formula II, R<sub>6</sub> represents hydrogen, methyl, ethyl, 1-adamantyl, phenyl, 2-(diethylamino)ethyl, 2-hydroxyethyl, 2,3-dihydroxypropyl, trifluoromethyl or benzyl. More preferably R<sub>6</sub> represents hydrogen, methyl, phenyl, 2-(diethylamino)ethyl, 2-hydroxyethyl, 2,3-dihydroxypropyl. Most preferably R<sub>6</sub> represents hydrogen, methyl or 2-hydroxyethyl.  
25

In preferred compounds of formula II, R<sub>7</sub> represents hydrogen, 2'-methyl, 3'-methyl, 3'-methoxy, 3'-chloro or 3'-carboxy. More preferably R<sub>7</sub> represents hydrogen, 2'-  
30



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methyl, 3'-methyl or 3'-methoxy. Most preferably R<sub>7</sub> represents hydrogen or 3'-methyl.

In preferred compounds of formula II, R<sub>8</sub> represents hydrogen, 5'-methyl, 5'-methoxy or 5'-chloro. More preferably R<sub>8</sub> represents hydrogen, 5'-methyl or 5'-methoxy. Most preferably R<sub>8</sub> represents hydrogen or 5'-methyl.

In preferred compounds of formula II, R<sub>9</sub> represents hydrogen or methyl. More preferably R<sub>9</sub> represents hydrogen.

One group of more preferred compounds of formula I is represented by formula II in which

R<sub>1</sub> represents hydrogen, a C<sub>1-4</sub> alkyl group or 2-carboxyvinyl;

R<sub>2</sub> represents a C<sub>2-4</sub> alkoxy group;

R<sub>3</sub> represents hydrogen;

R<sub>4</sub> represents a C<sub>3-4</sub> alkoxy carbonyl group;

R<sub>5</sub> represents hydrogen;

R<sub>6</sub> represents a C<sub>1-4</sub> alkyl group, phenyl, benzyl, trifluoromethyl, 2-hydroxyethyl, 2-(diethylamino)ethyl, 2,3-dihydroxypropyl;

R<sub>7</sub> represents hydrogen or 2'-methyl and R<sub>8</sub> and R<sub>9</sub> represent hydrogen.

A second group of more preferred compounds of formula I is represented by formula II in which

R<sub>1</sub> represents hydrogen, hydroxy, ethoxy or trifluoromethyl;

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R<sub>2</sub> represents hydrogen;

R<sub>3</sub> represents hydrogen;

R<sub>4</sub> represents a C<sub>3-4</sub> alkoxy carbonyl group;

R<sub>5</sub> represents hydrogen;

- 5 R<sub>6</sub> represents a C<sub>1-4</sub> alkyl group (which may be optionally substituted by one or more of the following: hydroxy, halo or an amino group of formula -NR<sub>12</sub>R<sub>13</sub> in which R<sub>12</sub> and R<sub>13</sub> independently represents hydrogen or a C<sub>1-4</sub> alkyl group); and
- 10 R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> each represent hydrogen.

A third group of more preferred compounds of formula I is represented by formula II in which

R<sub>1</sub> represents a C<sub>1-4</sub> alkyl group;

R<sub>2</sub> represents a C<sub>2-4</sub> alkoxy group;

- 15 R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> represent hydrogen;

R<sub>7</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group;

R<sub>8</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group; and

R<sub>9</sub> represents hydrogen.

Specific compounds of formula I are:

- 20 Ethyl 6-ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylate
- 3-Ethoxy-5-(4-methoxyanilino)-2-methyl-1,8-naphthyridine

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Ethyl 4-(4-methoxyanilino)-7-trifluoromethyl-1,8-naphthyridine-3-carboxylate

Ethyl 6-ethoxy-4-(4-methoxyanilino)-1,8-naphthyridine-3-carboxylate

5 3-Butyryl-6-ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine

Ethyl 7-ethoxy-4-(4-methoxyanilino)-1,8-naphthyridine-3-carboxylate

10 Ethyl 6-bromo-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylate

3-Bromo-5-(4-methoxyanilino)-2-methyl-1,8-naphthyridine

Ethyl 6-ethoxy-4-[4-(2-hydroxyethoxy)anilino]-7-methyl-1,8-naphthyridine-3-carboxylate

15 Ethyl 6-ethoxy-4-(4-methoxy-2-methylanilino)-7-methyl-1,8-naphthyridine-3-carboxylate

3-Ethoxy-5-(4-methoxy-2-methylanilino)-2-methyl-1,8-naphthyridine

4-[4-(2-Diethylaminoethoxy)anilino]-6-ethoxy-7-methyl-1,8-naphthyridine

20 4-(6-Ethoxy-7-methyl-1,8-naphthyridin-4-ylamino)-2,6-xyleneol

5-[4-(1-Adamantyloxy)anilino]-3-ethoxy-2-methyl-1,8-naphthyridine

3-Ethoxy-5-(2-methoxyanilino)-2-methyl-1,8-naphthyridine

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- Ethyl 6-ethoxy-4-(4-ethoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylate
- Ethyl 6-ethoxy-7-methyl-4-(4-trifluoromethoxyanilino)-1,8-naphthyridine-3-carboxylate
- 5 Ethyl 4-(4-benzyloxyanilino)-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxylate
- Ethyl 4-[4-(2,3-dihydroxypropoxy)anilino]-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxylate
- Ethyl 6-ethoxy-4-(4-hydroxy-3-methylanilino)-7-methyl-1,8-naphthyridine-3-carboxylate
- 10
- Ethyl 4-[4-(2-diethylaminoethoxy)anilino]-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxylate
- Ethyl 6-ethoxy-4-(4-methoxy-3,5-dimethylanilino)-7-methyl-1,8-naphthyridine-3-carboxylate
- 15 2,6-Dichloro-4-(6-ethoxy-7-methyl-1,8-naphthyridin-4-ylamino)phenol
- 6-Ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxamide
- Ethyl 4-(4-methoxyanilino)-7-methyl-6-propoxy-1,8-naphthyridine-3-carboxylate
- 20
- Ethyl 6-methoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylate
- 6-Bromo-3-ethoxy-5-(4-methoxyanilino)-2-methyl-1,8-naphthyridine
- 25 5-(6-Ethoxy-3-ethoxycarbonyl-7-methyl-1,8-naphthyridin-4-ylamino)salicylic acid

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- 3-Ethoxy-5-(4-methoxyanilino)-2,7-dimethyl-1,8-naphthyridine
- 3-Ethoxy-5-(4-methoxyanilino)-2,6-dimethyl-1,8-naphthyridine
- 5 Ethyl 6-ethoxy-7-methyl-4-(3,4,5-trimethoxyanilino)-1,8-naphthyridine-3-carboxylate
- 3-[4-(6-Ethoxy-7-methyl-1,8-naphthyridin-4-ylamino)-phenoxy]propane-1,2-diol
- 3-Ethoxy-2-methyl-5-(4-phenoxyanilino)-1,8-naphthyridine
- 10 Ethyl 6-ethoxy-7-methyl-4-(4-phenoxyanilino)-1,8-naphthyridine-3-carboxylate
- 4-(6-Ethoxy-7-methyl-1,8-naphthyridine-4-ylamino)phenol
- Ethyl 6-ethoxy-4-(4-methoxy-N-methylanilino)-7-methyl-1,8-naphthyridine-3-carboxylate
- 15 6-Ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridin-3-ylmethanol
- 3-[3-Ethoxy-5-(4-methoxyanilino)-1,8-naphthyridin-2-yl]acrylic acid
- 3-[3-Ethoxy-6-ethoxycarbonyl-5-(4-methoxyanilino)-1,8-naphthyridin-2-yl]acrylic acid
- 20 3-[3-Ethoxy-6-ethoxycarbonyl-5-(4-methoxyanilino)-1,8-naphthyridin-2-yl]propionic acid
- 6-Ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylic acid

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Ethyl 4-[4-methoxyanilino]-7-oxo-7,8-dihydro-1,8-naphthyridine-3-carboxylate

5-(4-Methoxyanilino)-1,8-naphthyridin-2-ylmethanol

1-[6-Ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridin-3-yl]butan-1-ol

6-Hydroxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylic acid

and pharmaceutically acceptable salts thereof, in the form of individual enantiomers, racemates or other mixtures of enantiomers.

When a compound of formula I contains a single chiral centre it may exist in two enantiomeric forms. The present invention includes individual enantiomers and mixtures of those enantiomers. The enantiomers may be obtained by methods known to those skilled in the art. Such methods typically include resolution via formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallisation; resolution via formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer by reaction with an enantiomer-specific reagent, for example, enzymatic esterification, oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation processes described above, a further step will subsequently be required to liberate the desired

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enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other  
5 by asymmetric transformation.

When a compound of formula I contains more than one chiral centre it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example,  
10 chromatography or crystallisation and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of formula I or II and mixtures thereof.

15 Certain compounds of formula I may exist in different tautomeric forms which fall within the scope of the present invention.

Some compounds of formula I may exist in the form of solvates, for example, hydrates, which also fall  
20 within the scope of the present invention.

The compounds of formula I may form organic or inorganic salts, for example, the compounds of formula I may form acid addition salts with inorganic or organic acids, e.g. hydrochloric acid, hydrobromic acid, fumaric  
25 acid, tartaric acid, citric acid, sulphuric acid, hydriodic acid, maleic acid, acetic acid, succinic acid, benzoic acid, pamoic acid, palmitic acid, dodecanoic acid and acidic amino acids such as glutamic acid. Some compounds of formula I may form base addition salts, for  
30 example, with alkali metals for example sodium hydroxide, or with aminoacids for example, lysine or arginine. It will be appreciated that such salts, provided they are pharmaceutically acceptable may be used in therapy in place of the corresponding compounds

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of formula I. Such salts are prepared by reacting the compound of formula I with a suitable acid or base in a conventional manner. Such salts may also exist in form of solvates (for example, hydrates).

- 5        Certain compounds of formula I may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof.

10        The present invention also provides pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I together with a pharmaceutically acceptable diluent or carrier. Such pharmaceutical formulations may be used in the treatment of rheumatic diseases for example rheumatoid arthritis or osteoarthritis.

- 15        As used hereinafter, the term "active compound" denotes a 1,8-naphthyridine of formula I. In therapeutic use, the active compound may be administered orally, rectally, parenterally, topically, ocularly, aurally, nasally, intravaginally or to the buccal  
20        cavity, to give a local and/or systemic effect. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for such methods of administration. The compositions may be formulated in a manner known to  
25        those skilled in the art so as to give a controlled release, for example rapid release or sustained release, of the compounds of the present invention. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy.  
30        The compositions of the invention may contain 0.1-90% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of active ingredient is 1-500 mg. The excipients used in the preparation of these



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compositions are the excipients known in the pharmacist's art.

Compositions for oral administration are preferred compositions of the invention and there are known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oily suspensions.

Tablets may be prepared from a mixture of the active compound with fillers such as lactose or calcium phosphate, disintegrating agents, for example maize starch, lubricating agents, for example magnesium stearate, binders for example microcrystalline cellulose or polyvinyl pyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate.

Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods, and, if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 0.1 to 1000 mg (for example 10 mg, 50 mg, 100 mg, 200 mg, 400 mg or 800 mg) of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions

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containing a compound of the present invention in a suitable vegetable oil, for example sunflower oil.

The active compound may be formulated into granules with or without additional excipients. The granules may  
5 be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules may contain disintegrants (for example a pharmaceutically acceptable effervescent couple formed from an acid and a carbonate or  
10 bicarbonate salt) to facilitate dispersion in the liquid medium.

Compositions for topical administration are also preferred compositions of the invention. The pharmaceutically active compound may be dispersed in a  
15 pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating the active compound in a topical vehicle such as petrolatum and/or light liquid paraffin, dispersed in an aqueous medium using surfactants. An ointment may be prepared  
20 by mixing the active compound with a topical vehicle such as a mineral oil, petrolatum and/or a wax e.g. paraffin wax or beeswax. A gel may be prepared by mixing the active compound with a topical vehicle comprising a gelling agent e.g. basified Carbomer BP, in  
25 the presence of water. Topically administrable compositions may also comprise a matrix in which the pharmaceutically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the  
30 compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as described above, together with a potential transdermal accelerant such as dimethyl sulphoxide or  
35 propylene glycol.

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Compositions of the invention suitable for rectal administration are known pharmaceutical forms for such administration, for example suppositories with hard fat, synthetic glycerides or polyethylene glycol bases.

- 5        Compositions of the invention suitable for parenteral administration are known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

- 10       Compositions of the invention suitable for inhalation via the mouth and/or the nose are the known pharmaceutical forms for such administration, for example aerosols, nebulised solutions or powders. Metered dose systems, known to those skilled in the art, may be used.

- 15       Compositions suitable for application to the buccal cavity include slow dissolving tablets, troches, chewing gum, gels, pastes, powders, mouthwashes or rinses.

- 20       The compounds of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion, or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may
- 25       be a) liquid such as an oily solution or suspension of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or b) solid in the form of an implanted support for example of a synthetic resin of waxy
- 30       material for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered.
-

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In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

- 5        In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients, for example, a non-steroidal antiinflammatory agent e.g. ibuprofen, S(+)-ibuprofen, flurbiprofen or S(+)-  
10 flurbiprofen, an analgesic or an antipyretic agent.

- The compounds of formula I are indicated for use as anti-rheumatic agents by their activity demonstrated by means of tests on standard laboratory animals. Such tests include, for example, the oral administration of  
15 compounds of formula I to mice with experimental antigen-induced arthritis. Compounds of formula I are suitable for use in treating rheumatic diseases for example rheumatoid arthritis, osteoarthritis, osteoporosis, crystal arthropathies (e.g. gout),  
20 reactive arthritis, ankylosing spondylitis or psoriatic arthropathy.

Compounds of formula I may also be suitable for the treatment of diseases of the oral cavity for example periodontitis, gingivitis and alveolar bone resorption.

- 25        Accordingly, in a further aspect, the present invention also includes a method of treating rheumatic diseases, particularly rheumatoid arthritis and osteoarthritis, comprising the administration of a therapeutically effective amount of a compound of  
30 formula I to a mammal in need thereof. Compounds of formula I may also be administered in a prophylactic manner to mammals, particularly humans who have been identified as being susceptible to arthritic diseases.

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Whilst the precise amount of active compound administered will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history and always lies within the sound discretion of the administering physician, a suitable dose for oral administration to mammals, including humans, is generally within the range 0.01-80 mg/kg/ day, more usually 0.2-40 mg/kg/day given in single or divided doses. For parenteral administration, a suitable dose is generally within the range 0.001-80 mg/kg/day, more usually 0.2-40 mg/kg/day given in single or divided doses or by continuous infusion. A suitable preparation for topical administration generally contains the active ingredient within the range 0.01-20% by weight, more usually 0.05-5% by weight. Oral administration is preferred.

The pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I may be used to treat rheumatic diseases such as rheumatoid arthritis and osteoarthritis. In such treatment the amount of the compound of formula I administered per day is in the range 0.1 to 6000 mg.

In yet another aspect, the present invention provides the use of a compound of formula I in the manufacture of a medicament for use in the treatment of a rheumatic disease such as rheumatoid arthritis and osteoarthritis.

Processes for the preparation of compounds of formula I will now be described. These processes form a further aspect of the present invention.

Compounds of formula I in which  $R_1$  represents a carboxy  $C_{2-4}$  alkyl group may be prepared by reducing a compound of formula I in which  $R_1$  represents a carboxy  $C_{2-4}$  alkenyl group, for example with a reducing agent,

- 20 -

e.g. hydrogen in the presence of a catalyst e.g. palladium.

Compounds of formula I in which  $R_1$  represents hydroxy may be prepared by hydrolysis of a compound of formula I in which  $R_1$  represents a  $C_{1-6}$  alkoxy group, for example using a base e.g. sodium hydroxide.

Compounds of formula I in which  $R_4$  represents an  $\alpha$ -hydroxy  $C_{1-6}$  alkyl group may be prepared by reducing a compound of formula I in which  $R_4$  represents a  $C_{2-7}$  alkoxy carbonyl group or a  $C_{1-6}$  alkanoyl group, by methods known to those skilled in the art, for example using lithium aluminium hydride or lithium triethylborohydride.

Compounds of formula I in which  $R_2$  represents hydroxy may be prepared by reacting a compound of formula I in which  $R_2$  represents a  $C_{1-6}$  alkoxy group with a de-alkylating agent for example aluminium chloride.

Compounds of formula I in which  $R_4$  represents carboxy may be prepared by hydrolysis of compounds of formula I in which  $R_4$  represents a  $C_{2-6}$  alkoxy carbonyl group by methods known to those skilled in the art, for example using an acid e.g. hydrochloric acid or a base e.g. sodium hydroxide.

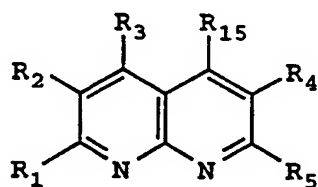
Compounds of formula I in which  $R_1$  represents an  $\omega$ -hydroxy  $C_{1-6}$  alkyl may be prepared by reducing a compound of formula I in which  $R_1$  represents a  $C_{2-6}$  alkoxy carbonyl group or a  $C_{2-6}$  alkoxy carbonyl  $C_{1-4}$  alkyl group by methods known to those skilled in the art for example using lithium aluminium hydride or lithium triethylborohydride.

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Compounds of formula I in which  $R_1$  represents a carboxyvinyl group may be prepared by reacting compounds of formula I in which  $R_1$  represents methyl with glyoxylic acid for example by heating together  
 5 optionally in the presence of a catalyst e.g. trifluoroacetic acid.

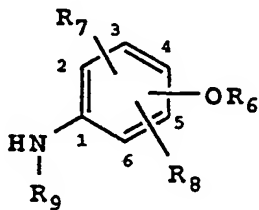
Compounds of formula I in which  $R_6$  represents a group other than hydrogen may be prepared by reacting a compound of formula I in which  $R_6$  represents hydrogen  
 10 with a compound of formula  $R_6L$  (XVI) in which L represents a leaving group for example halo, for example by heating, optionally in the presence of an inert organic liquid which is preferably a solvent for the reactants e.g. *N,N*-dimethylformamide at a temperature in  
 15 the range 0-150°C, preferably in the range 30-120°C, at atmospheric pressure, preferably in the presence of a base for example sodium hydride.

Compounds of formula I may be prepared by reacting a compound of formula III



III

20 in which  $R_{15}$  represents a leaving group, including halo, e.g. bromo or chloro; mercapto or methylthio with a compound of formula IV

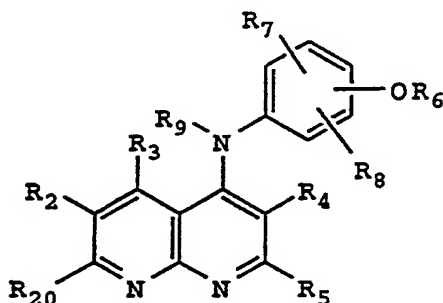


IV

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or a salt thereof by heating, optionally in the presence of an inert organic liquid which is preferably a solvent for the reactants, e.g. an alcohol or an ether, at a temperature in the range 0-150°C, preferably in the range 30-120°C, at atmospheric pressure, optionally in the presence of an acid, for example hydrochloric acid, or a base, for example sodium carbonate or sodium bicarbonate.

Compounds of formula I in which  $R_1$  represents a  $C_{1-6}$  alkoxy group may be prepared by reacting a compound of formula XVII



X V I I

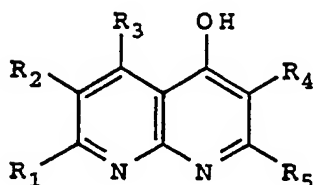
in which  $R_{20}$  represents a leaving group, for example halo, with an alkali metal  $C_{1-6}$  alkoxide, by heating optionally in the presence of an inert organic liquid which is preferably a solvent for the reactants, for example an alcohol, at a temperature in the range 50-250°C preferably 150-200°C preferably in a sealed vessel under pressure.

Compounds of formula I in which  $R_1$  represents hydroxy may be prepared by displacing  $R_{20}$  from a compound of formula XVII, in which  $R_{20}$  represents a leaving group, for example halo, with a hydroxy group, for example by reacting with an alkali metal hydroxide in the presence of an inert organic liquid or by hydrolysis using an aqueous acid or base, at a temperature in the range 0-200°C.



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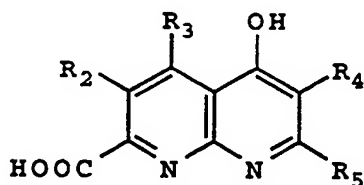
Compounds of formula III in which  $R_{15}$  represents halo may be prepared by reacting compounds of formula V



V

with a halogenating agent for example phosphorus oxychloride or phosphorus oxybromide at a temperature in the range 0-150°C, preferably 20-100°C, optionally in the presence of an inert organic liquid which is preferably a solvent for the reactants. Compounds of formula III in which  $R_{15}$  represents mercapto or methylthio may be prepared from compounds of formula V by methods known to those skilled in the art.

Compounds of formula V in which  $R_1$  represents hydrogen may be prepared by the thermal decarboxylation of compounds of formula VI

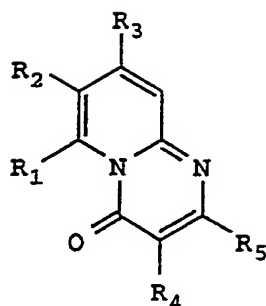


VI

for example by heating at a temperature in the range 100-350°C in a suitable organic liquid e.g. diphenyl ether, quinoline or liquid petrolatum.

Compounds of formula V in which  $R_1$  represents a substituent other than hydrogen may be prepared by heating compounds of formula VII

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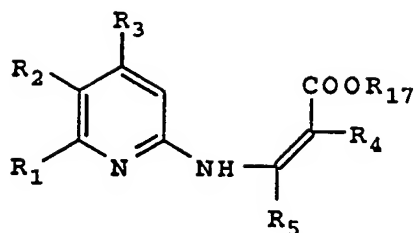
V II

in which  $R_1$  represents a substituent other than hydrogen in the presence of a suitable solvent, for example diphenyl ether or liquid petrolatum at a temperature in the range 150 to 350°C.

- 5 Compounds of formula V in which  $R_4$  represents hydrogen may be prepared by heating compounds of formula V in which  $R_4$  represents  $\text{COOR}_{16}$  and  $R_{16}$  represents hydrogen or a  $\text{C}_{1-4}$  alkyl group, with aqueous sodium hydroxide solution in a sealed vessel or by thermal
- 10 decarboxylation of compounds of formula V in which  $R_{16}$  represents hydrogen optionally in the presence of an organic liquid, for example quinoline or liquid petrolatum.

- 15 Compounds of formula VI may be prepared by oxidising compounds of formula V in which  $R_1$  represents a  $\text{C}_{1-6}$  alkyl group, for example with selenium dioxide, or by oxidising compounds of formula V in which  $R_1$  represents a carboxyvinyl group for example with potassium permanganate.

- 20 Compounds of formula VII may be prepared by heating compounds of formula VIII

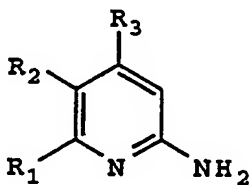


V III

in which  $R_{17}$  represents a  $C_{1-4}$  alkyl group in the presence of a suitable solvent, for example diphenyl ether or liquid petrolatum at a temperature in the range 150 to 350°C, or by reacting compounds of formula VIII  
 5 with phosphorus oxychloride in the presence of polyphosphoric acid.

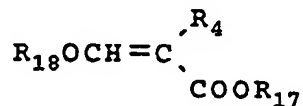
Compounds of formula VIII, in which  $R_1$  represents a substituent as defined above, other than hydrogen, may be heated in the presence of an organic liquid, for  
 10 example diphenyl ether or liquid petrolatum at a temperature in the range of 150 to 350°C to produce compounds of formula V.

Compounds of formula VIII in which  $R_5$  represents hydrogen may be prepared by reacting a compound of  
 15 formula IX



IX

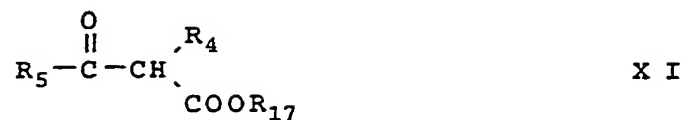
with a compound of formula X



X

in which  $R_{17}$  or  $R_{18}$  independently represent a  $C_{1-4}$  alkyl group or with a compound of formula XI

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or a salt thereof, e.g. the sodium salt, in which  $\text{R}_{17}$  represents a  $\text{C}_{1-4}$  alkyl group, in the presence of a suitable solvent, for example ethanol, at a temperature in the range 50 to 200°C.

- 5        Compounds of formula VIII in which  $\text{R}_5$  represents hydrogen may also be prepared by reacting a compound of formula IX with a tri( $\text{C}_{1-4}$  alkyl)orthoformate and a compound of formula  $\text{R}_4\text{CH}_2\text{CO}_2\text{R}_{17}$ , for example by heating, optionally in the presence of a solvent for example  
 10    acetic anhydride and/or a Lewis acid catalyst for example zinc chloride.

Compounds of formulae IX, X and XI may be prepared by methods known to those skilled in the art.

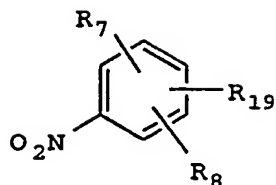
Compounds of formula XII



- 15    may be reduced for example, by heating in the presence of reduced iron powder and dilute acid, to prepare compounds of formula IV, in which  $\text{R}_9$  represents hydrogen.

- 20    Compounds of formula XII in which  $\text{R}_6$  represents an optionally substituted  $\text{C}_{1-6}$  alkyl group or an optionally substituted phenyl group and  $\text{OR}_6$  is located ortho or para to the nitro group may be prepared by reacting a compound of formula XIII

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X III

in which  $R_{19}$  represents halo and is located ortho or para to the nitro group, respectively, with a salt of formula XIV

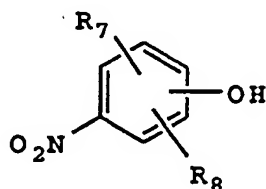


X IV

in which  $R_6$  represents an optionally substituted  $C_{1-6}$  alkyl group or a phenyl group, which may be optionally substituted, and M represents an alkali metal, for example sodium or potassium, for example by heating, optionally in the presence of an organic liquid, which is preferably a solvent for the reactants, for example

10  $R_6OH$ .

Compounds of formula XII in which  $R_6$  represents an optionally substituted alkyl group may be prepared by alkylating a compound of formula XV



X V

by methods known to those skilled in the art for example

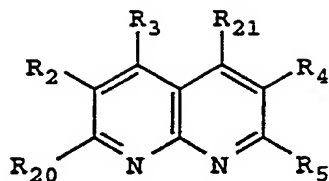
15 by reaction with a compound of formula  $R_6L$  (XVI) in which L represents a leaving group for example halo.

Compounds of formulae XIII, XIV, XV and XVI may be prepared by methods known to those skilled in the art.

Compounds of formula XVII may be prepared by

20 reacting a compound of formula XVIII

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X V I I I

in which R<sub>21</sub> represents halo, for example chloro or bromo, with a compound of formula IV using conditions analogous to those described for the preparation of compounds of formula I from a compound of formula III  
5 and a compound of formula IV.

Compounds of formula XVIII may be prepared by processes analogous to those described for the preparation of compounds of formula III.

Certain intermediate compounds of formulae III-X  
10 inclusive are believed to be novel compounds. All novel compounds herein form a further aspect of the invention.

The therapeutic activity of the compounds of the present invention has been demonstrated by tests which include the oral administration of the compounds to mice  
15 with experimental antigen-induced arthritis. The compounds showed activity in the following test:

Female BALB/c mice, 8 weeks of age were used: each control group contained either 35 or 80 mice and each test group contained either 13 or 20 mice respectively.  
20 The mice were sensitised by subcutaneous injection into the flank with an emulsion (0.1 ml) consisting of a solution of methylated bovine serum albumin (m-BSA) (0.1 mg) in sterile aqueous sodium chloride solution (0.05 ml; 0.15 M) and Complete Adjuvant (0.05 ml) containing,  
25 in total, Mycobacterium (0.075 mg). Simultaneously each mouse was injected intraperitoneally with an aqueous suspension of heat killed Bordetella Pertussis (0.05 ml;

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2 x 10<sup>9</sup> organisms). Identical injections were administered after 7 days. After a further 14 days the left knee-joint of each mouse was injected with a solution of m-BSA (0.1 mg) in aqueous sodium chloride solution (0.01 ml; 0.15 M) (intra-articular challenge). This procedure induced a chronic erosive arthritis restricted to the challenged joint.

The test compounds were suspended in a vehicle of aqueous carboxymethyl cellulose solution (0.25% w/v) containing TWEEN®80 (1.5% w/v) at varying dosages and 0.1 ml was administered to each test mouse by gastric intubation. The control mice received the vehicle with no test compound. Administration occurred daily for 28 days commencing 14 days after intra-articular challenge. After 42 days the test was terminated and the animals were killed using a rising concentration of carbon dioxide and the arthritic hind leg removed.

The femur and tibia were cut midway along their length and the knee-joint trimmed free of skin and musculature. The arthritic joints were placed in perforated plastic holders and fixed in 10% formol saline for at least 48 hours. They were then decalcified in 5% formic acid for 72 hours with constant agitation (replacing the formic acid after the first 24 hours), washed in water, dehydrated in alcohol and embedded in paraffin wax. The joints were sectioned in the sagittal plane at 5 µm and stained with Van Gieson's stain. Each joint was sectioned at two levels.

The severity of arthritis was assessed by examination of the prepared sections. Synovitis and pannus formation were graded on a 0-5 scale, by a skilled operator, according to the degree of synovial lining cell hypertrophy and hyperplasia, infiltration of the synovium by lymphocytes, plasma cells, monocytes/macrophages, fibroblasts and polymorpho-

- 30 -

nuclear (PMN) leukocytes and the degree of pannus formation. Erosions of cartilage and bone were also graded on a 0-5 scale, by a skilled operator, the score reflecting the proportion of articular surface eroded as well as the depth of the erosions. Using the combined data the drug effects were expressed as the percentage change in the mean scores for synovitis and erosions compared to those of the control group. The data were then analysed using the Mann-Whitney U-test.

10        Those compounds which induced a statistically significant suppression of erosions or synovitis at a dosage of 100 mg/kg or below were deemed to be active. The results obtained are given in the Examples.

15        As an alternative to histological assessments, analysis of macerated specimens of tibial epiphyses using an image analysis system, may be used to assess the extent of hard tissue erosions. Active compounds are those which significantly reduce these erosions.

20        The invention is illustrated by the following non-limitative Examples in which parts and percentages are by weight and compositions of mixed solvents are given by volume. Novel compounds were characterised by elemental analysis and one or more of the following spectroscopic techniques: nuclear magnetic resonance, 25    infra-red and mass spectroscopy.

      In the Examples the following abbreviations are used: IMS = industrial methylated spirit and DMF = N,N-dimethylformamide.

30        Unless otherwise stated, the starting materials used in the Examples were commercially available and may be obtained by reference to the Fine Chemicals Directory.



Preparation of Starting Materials and IntermediatesExample A1

a) Sodium metal (46.2 g) was dissolved in absolute ethanol (1 l) with stirring under nitrogen. 3-Hydroxy-2-methylpyridine (200 g prepared as described in C.A. 48, P4597 h) was added. The mixture was stirred at ambient temperature for 30 minutes and then a solution of bromoethane (150 ml) in absolute ethanol (100 ml) was added. The mixture was boiled under reflux for 5 hours then cooled and filtered. The filtrate was evaporated and the residue partitioned between dichloromethane and water. The organic layer was separated off and the aqueous layer extracted with dichloromethane. The combined organic extracts were dried and evaporated. The residue was distilled to give 3-ethoxy-2-methylpyridine b.p. 80-84°C (20 mmHg).

b) 3-Ethoxy-2-methylpyridine (132.5 g) was added dropwise to concentrated sulphuric acid (530 ml) with stirring and cooling to keep the mixture below 10°C. A mixture of concentrated nitric acid (81 ml) and concentrated sulphuric acid (97 ml) was added dropwise over 4 hours, keeping the temperature below 5°C. The reaction mixture was allowed to warm up slowly to ambient temperature and then added in portions to ice/water (2.5 l). The solid was collected by filtration, washed with water and dried under vacuum at 50°C to give 3-ethoxy-2-methyl-6-nitropyridine, m.p. 82-84°C.

c) The nitropyridine above (176 g), IMS (1.6 l), reduced iron powder (179 g) and water (350 ml) were boiled under reflux. Heating was discontinued while concentrated hydrochloric acid (67 ml) was carefully added dropwise over 20 minutes. The mixture was boiled under reflux for 1.75 hours then cooled and filtered

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through a filtration aid. The filtrate was evaporated under reduced pressure. Water was added to the residue and the mixture basified with 5M sodium hydroxide. Extractive work-up (dichloromethane) gave 5-ethoxy-6-methylpyridin-2-amine, m.p. 93-96°C.

d) A mixture of the amine from (c) above (138 g) and diethyl ethoxymethylenemalonate (196 g) in IMS (190 ml) was boiled under reflux for 3 hours. The mixture was cooled and filtered to give diethyl 2-(5-ethoxy-6-methylpyrid-2-ylaminomethylene)malonate, m.p. 132-138°C.

e) The malonate (118.3 g) from (d) above was added to boiling diphenyl ether (1.5 l) over 10 minutes with stirring while allowing the ethanol formed to be removed by downward distillation. The mixture was boiled under reflux for 1.5 hours then cooled and diluted with petroleum ether b.p. 60-80°C (1.5 l). The solid was collected by filtration and washed with petroleum ether b.p. 60-80°C to give ethyl 6-ethoxy-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate, m.p. 255-258°C.

f) A mixture of ethyl 6-ethoxy-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (7.5 g), sodium hydroxide pellets (1.2 g) and water (20 ml) was heated at 180°C with stirring in a sealed reaction vessel for 16 hours. The mixture was cooled to ambient temperature, filtered and the residue washed with water to give, after drying, 6-ethoxy-7-methyl-1,8-naphthyridin-4-ol, m.p. 278-282°C (with decomposition).

#### Example A2

a) A mixture of 2-chloro-6-trifluoromethylpyridine (20.0 g), cuprous chloride (0.2 g) and ammonia (specific gravity 0.88, 75 ml) was heated at 170°C in a pressure vessel for 18 hours. After cooling to ambient temperature, the mixture was extracted with

- 33 -

dichloromethane (300 ml). The organic extract was dried and evaporated to give 6-trifluoromethylpyridin-2-amine, m.p. 74-79°C.

b) A mixture of 6-trifluoromethylpyridin-2-amine  
5 (17.2 g) and diethyl ethoxymethylenemalonate (22.9 g) was heated at 95°C, under vacuum for 8 hours. The mixture was cooled and diluted with petroleum ether b.p. 60-80°C (50 ml). The mixture was filtered and the residue was recrystallised from IMS to give diethyl 2-  
10 (6-trifluoromethyl-2-pyridylaminomethylene)malonate, m.p. 125-128°C.

c) The above malonate (22.55 g) was added dropwise with stirring to boiling diphenyl ether (250 ml) under reflux. The mixture was boiled for 2 hours, then cooled  
15 and diluted with petroleum ether b.p. 60-80°C. The solid was collected by filtration to give ethyl 4-hydroxy-7-trifluoromethyl-1,8-naphthyridine-3-carboxylate, m.p. >250°C.

#### Example A3

20 a) A mixture of ethyl 6-ethoxy-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (2.8g), glyoxylic acid monohydrate (1.5g) acetic acid (20ml) and trifluoroacetic acid (10ml) was heated at 90-95°C for 2 hours, with stirring. The mixture was evaporated down under  
25 reduced pressure. The residue was triturated with hot ethanol and filtered to give 3-(3-ethoxy-6-ethoxycarbonyl-5-hydroxy-1,8-naphthyridin-2-yl)acrylic acid, m.p. >280°C.

b) A solution of the acrylic acid from a) above (10g)  
30 in t-butanol (2.2l) was formed by boiling the mixture under reflux with stirring. Heating was discontinued and a solution of potassium carbonate (8.9g) in water (250ml) was added rapidly dropwise. A solution of

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sodium periodate (62g) in water (600ml), preheated to 60°C, was added in portions over 2 hours. A solution of potassium permanganate (0.72g) in water (500ml) was added dropwise until a purple colour was obtained. The resultant mixture was stirred at ambient temperature for 7 hours adding more permanganate as required to retain the purple colour. The mixture was boiled under reflux and the remaining permanganate solution added. The mixture was then stirred at ambient temperature for 16 hours. Solid sodium metabisulphite was added until the mixture was colourless. The t-butanol was removed under reduced pressure. The residue was diluted with water (500ml) and acidified with concentrated hydrochloric acid. On extracting this mixture with dichloromethane, a solid precipitated and this was collected by filtration. This solid was added to dilute sodium bicarbonate solution and the insoluble impurities removed by filtration. The filtrate was acidified and on shaking with dichloromethane a solid precipitated. This solid was collected by filtration to give 3-ethoxy-6-ethoxycarbonyl-5-hydroxy-1,8-naphthyridine-2-carboxylic acid, m.p.270-272°C.

c) The acid from b) above (1.0g) was added in portions to boiling diphenyl ether (100ml) with stirring under reflux. The mixture was boiled for 10 minutes after the addition and then cooled to ambient temperature. Petroleum ether b.p. 60-80°C was added and the solid collected by filtration to give ethyl 6-ethoxy-4-hydroxy-1,8-naphthyridine-3-carboxylate dihydrate, m.p.262-264°C.

#### Example A4

a) A mixture of ethyl butyrylacetate (105.1 g), acetic anhydride (126 ml) and triethylorthoformate (117 ml) was stirred and boiled under reflux for 1.5 hours. The low boiling materials were distilled off under reduced

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pressure and the residue distilled under high vacuum to give ethyl 2-(ethoxymethylene)-3-oxohexanoate, b.p. 109-120°C (0.4 mmHg).

b) Ethyl 2-(ethoxymethylene)-3-oxohexanoate (22.4 g) was added to a suspension of 5-ethoxy-6-methylpyridin-2-amine (14.9 g) in IMS (50 ml). After the initial exotherm had subsided IMS (100 ml) was added and the mixture boiled under reflux until a solution was obtained. This solution was cooled and filtered to give ethyl 2-(5-ethoxy-6-methylpyrid-2-ylaminomethylene)-3-oxohexanoate, m.p. 117-120°C.

c) The product from b) (28 g) was added in portions over 3 minutes with stirring to diphenyl ether (500 ml) at 250°C. The mixture was boiled under reflux for 2 hours, cooled, diluted with petroleum ether b.p. 40-60°C (400 ml) and filtered to give 1-(6-ethoxy-4-hydroxy-7-methyl-1,8-naphthyridin-3-yl)-1-butanone, m.p. 240-241°C.

#### Example A5

a) A mixture of 6-ethoxypyridin-2-amine (8.0 g) and diethyl ethoxymethylenemalonate (12.5 g) was heated at 95°C under vacuum for 3 hours and then heated at 95°C at atmospheric pressure for 18 hours. The mixture was cooled to ambient temperature, diluted with petroleum ether b.p. 40-60°C and filtered to give diethyl (6-ethoxy-2-pyridylamino)methylenemalonate, m.p. 58-60°C.

b) The malonate from a) (15.3 g) was dissolved in diphenyl ether (50 ml) and added dropwise to boiling diphenyl ether (75 ml). The mixture was boiled under reflux for 45 minutes, then cooled and diluted with petroleum ether b.p. 60-80°C. The mixture was filtered to give ethyl 7-ethoxy-4-hydroxy-1,8-naphthyridine-3-carboxylate, m.p. 175-179°C.

Example A6

Ethyl 6-bromo-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate was prepared from 6-amino-3-bromo-2-methylpyridine (prepared by the bromination of 6-amino-2-methylpyridine) as described in UK 1,000,982.

Example A7

A mixture of ethyl 6-bromo-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (6.7 g), sodium hydroxide pellets (1.7 g) and water (50 ml) was heated at 180°C in a pressure vessel for 18 hours. The mixture was cooled and filtered to give 6-bromo-7-methyl-1,8-naphthyridin-4-ol, m.p. >250°C.

Example A8

This example was carried out in a similar manner to Example A1.

a) 3-Hydroxy-2-methylpyridine (50 g) was added to a solution of sodium (11.6 g) in propan-1-ol (250 ml) and the mixture treated with 1-bromopropane (51 ml) in propan-1-ol (50 ml) to give 2-methyl-3-propoxypyridine, b.p. 96-104°C (30 mmHg).

b) The propoxypyridine (30.0 g) was dissolved in concentrated sulphuric acid (100 ml) and treated with a mixture of concentrated nitric acid (17 ml) and concentrated sulphuric acid (20 ml) at 0-5°C to give 2-methyl-6-nitro-3-propoxypyridine, m.p. 54-56°C.

c) The nitropyridine (36.1 g), reduced iron powder (42.0 g), IMS (670 ml) and water (140 ml) were boiled and stirred under reflux while hydrochloric acid (15.3 ml) was added dropwise, to give 6-methyl-5-propoxypyridin-2-amine, as an oil.

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d) The product from (c) (17.9 g), diethyl ethoxymethylenemalonate (22 ml) and IMS (50 ml) were boiled under reflux for 2 hours to give diethyl 2-(6-methyl-5-propoxy-2-pyridylaminomethylene)malonate, m.p. 116-118°C.

e) The product from (d) (5 g) was added to diphenyl ether (100 ml) at 250°C with stirring and the mixture boiled for 1 hour under reflux to give ethyl 4-hydroxy-7-methyl-6-propoxy-1,8-naphthyridine-3-carboxylate, m.p. 231-5°C (with decomposition).

#### Example A9

This example was carried out in a similar manner to A1.

a) A mixture of sodium methoxide (prepared from sodium metal) (10.2 g) and methanol (175 ml), 3-hydroxy-2-methylpyridine (43.0 g) phenyltrimethylammonium chloride (81.9 g) and DMF (400 ml) was boiled under reflux with stirring for 5 hours under nitrogen. The mixture was filtered and distilled. The fraction boiling at 167-195°C was collected and purified by flash chromatography on silica using dichloromethane and then IMS as the mobile phase to give 3-methoxy-2-methylpyridine which was used without further purification.

b) The methoxypyridine (24.2 g) was dissolved in concentrated sulphuric acid (100 ml) and treated with a mixture of concentrated nitric acid (16.5 ml) and concentrated sulphuric acid (20.0 ml) which was added dropwise with stirring at 5°C, to give 3-methoxy-2-methyl-6-nitropyridine, m.p. 96-98°C.

c) The nitropyridine (18.0 g), reduced iron powder (24.4 g), IMS (390 ml) and water (82 ml) were boiled and stirred under reflux while concentrated hydrochloric acid

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(9.0 ml) was added cautiously, dropwise, to give 5-methoxy-6-methylpyridin-2-amine, m.p. 98-100°C.

d) A mixture of this pyridinamine (3.0 g), diethyl ethoxymethylenemalonate (4.4 ml) and IMS (10 ml) was  
5 boiled under reflux for 2 hours to give diethyl 2-(5-methoxy-6-methyl-2-pyridylaminomethylene)malonate, m.p. 109-110°C.

e) The malonate (6.2 g) was added to boiling diphenyl ether (140 ml) with stirring, and the mixture stirred at  
10 reflux for 45 minutes, to give ethyl 4-hydroxy-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxylate, m.p. 262-265°C.

#### Example A10

A mixture of 6-ethoxy-7-methyl-1,8-naphthyridin-4-  
15 ol, (5.0 g) in glacial acetic acid (60 ml) was stirred at between 15-20°C while a solution of bromine (2.4 ml) in glacial acetic acid (10 ml) was added dropwise over 10 minutes. The mixture was stirred at ambient temperature for 1.5 hours and then filtered. The  
20 residue was washed with water, ground up in water and the mixture basified with sodium bicarbonate and filtered. The solid obtained was ground in sodium bisulphite solution and filtered to give 3-bromo-6-ethoxy-7-methyl-1,8-naphthyridin-4-ol, m.p. 266-267°C.

#### 25 Example A11

A mixture of 5-ethoxy-6-methyl-pyridin-2-amine (22.0 g) and ethyl acetoacetate (22.4 ml) was stirred at ambient temperature while polyphosphoric acid (47 ml) was added slowly. After the addition the mixture was  
30 warmed gradually on a steam bath, with caution, until an exotherm occurred with considerable frothing. After the reaction had subsided the mixture was heated for 75



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minutes at 95°C, then cooled and added to ice/water. When all the polyphosphoric acid had dissolved the mixture was basified with 5M sodium hydroxide solution and the mixture extracted with dichloromethane to give

5 7-ethoxy-2,6-dimethylpyrido[1,2-a]pyrimidin-4-one m.p. 112-114°C. The pyrimidine (12.3 g) was added to stirred paraffin oil (190 ml) at 340°C over 10 minutes. The mixture was heated at 340°C for a further 40 minutes then cooled to ambient temperature and diluted with

10 petroleum ether, b.p. 60-80°C (180 ml). The mixture was filtered and the solid obtained was washed with ether. The solid was recrystallised from IMS to give 6-ethoxy-2,7-dimethyl-1,8-naphthyridin-4-ol, m.p. 281-4°C.

#### Example A12

15 a) A mixture of ethyl formate (55.2 g) and ethyl propionate (51.0 g) was added dropwise with stirring to a suspension of sodium hydride (20.9 g, 60% dispersion in mineral oil) in dry THF (260 ml) under nitrogen. On completion of the addition, the temperature of the

20 reaction mixture rose gradually from ambient temperature to 45°C accompanied by rapid evolution of hydrogen. The reaction mixture was stirred for 2 hours then cooled and water (400 ml) was added cautiously. The basic solution was washed with ether, then acidified with dilute

25 hydrochloric acid and extracted with ether to give an oil. The oil was distilled and the fraction boiling in the range 100-160°C was collected to give ethyl 2-formylpropionate.

b) The product from part a) (19.0 g) was added

30 dropwise to 5M sodium hydroxide solution (29 ml) and water (100 ml) keeping the temperature below 15°C. This solution was then added quickly to the solution of 5-ethoxy-6-methyl-pyridin-2-amine (20.0 g) in 4M hydrochloric acid (40 ml) and water (200 ml). This

35 mixture was stirred at ambient temperature for 2 hours

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then filtered to give a solid which was recrystallised from IMS/water to give ethyl 2-(5-ethoxy-6-methylpyridin-2-ylaminomethylene)propionate, m.p. 118-122°C.

- 5 c) The product from part b) (11.9 g) was added to paraffin oil (500 ml) at 320°C with stirring. Heating was continued at this temperature for 50 minutes and the reaction mixture allowed to cool. The mixture was poured into petroleum ether b.p. 40-60°C (1l) and the  
10 mixture filtered to give 6-ethoxy-3,7-dimethyl-1,8-naphthyridin-4-ol, m.p. 238-242°C.

#### Example A13

- A mixture of ethyl 6-ethoxy-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylate (10.0 g), 5M sodium  
15 hydroxide solution (200 ml), IMS (64 ml) and water (64 ml) was boiled under reflux for 2 hours. The mixture was cooled to ambient temperature and then filtered. The residue was dissolved in water, acidified to pH5 with glacial acetic acid and filtered. The  
20 residue was triturated with hot IMS, cooled and filtered to give 6-ethoxy-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid, m.p. 259-261°C.

#### Example B1

- Ethyl 6-ethoxy-4-hydroxy-7-methyl-1,8-naph-  
25 thyridine-3-carboxylate (2.5 g) was added to phosphorus oxychloride (20 ml) with stirring at ambient temperature. The mixture was warmed to 40°C and kept at this temperature for 1 hour then cooled to 10°C. The mixture was added to excess ice/water and the mixture  
30 basified with aqueous ammonia solution (specific gravity 0.88) while keeping the temperature below 5°C. The product was extracted into dichloromethane. The combined dichloromethane extracts were evaporated under

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reduced pressure at ambient temperature to give ethyl 4-chloro-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxylate, m.p. >250°C.

Example B2-B12

5           In a similar manner to that described in Example B1, a compound of formula V was treated with phosphorus oxychloride ( $\text{POCl}_3$ ) to produce a compound of formula III in which  $\text{R}_{15}$  represents chloro. The substituents  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$  and  $\text{R}_4$  on compounds of formula V and III and the  
10 reaction conditions are shown in Table 1.  $\text{R}_5$  is hydrogen in each example.

Table 1

	Substituents				Amt of Reactants			
Ex	R1	R2	R3	R4	Starting Compound IV (g)	POCl <sub>3</sub> (ml)	Reaction Temp (°C)	Reaction Time (minutes)
B2	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	H	H	2.5	25	60	60
B3	CF <sub>3</sub>	H	H	COOC <sub>2</sub> H <sub>5</sub>	3.4	30	90	75
B4	H	OC <sub>2</sub> H <sub>5</sub>	H	COOC <sub>2</sub> H <sub>5</sub>	2.0	40	50	120
B5	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	H	COC <sub>3</sub> H <sub>7</sub>	6.0	50	40-50	60
B6	OC <sub>2</sub> H <sub>5</sub>	H	H	COOC <sub>2</sub> H <sub>5</sub>	3.9	50	80	25
B7	CH <sub>3</sub>	Br	H	COOC <sub>2</sub> H <sub>5</sub>	3.5	20	30	60
B8	CO <sub>2</sub> CH <sub>3</sub>	H	H	H	35.9	150	60	120
B9	CH <sub>3</sub>	OC <sub>3</sub> H <sub>7</sub>	H	COOC <sub>2</sub> H <sub>5</sub>	1.8	15	40	60
B10	CH <sub>3</sub>	OCH <sub>3</sub>	H	COOC <sub>2</sub> H <sub>5</sub>	2.5	20	40	60
B11	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	H	Br	3.0	40	90	30
B12	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	H	CH <sub>3</sub>	3.5	30	95	90

Ex = Example    Amt = Amount    Temp = Temperature

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The compounds prepared in Examples B2-B12 were as follows:-

- B2: 5-Chloro-3-ethoxy-2-methyl-1,8-naphthyridine, m.p. 164°C.
- 5 B3: Ethyl 4-chloro-7-trifluoromethyl-1,8-naphthyridine-3-carboxylate, m.p. 250-252°C.
- B4: Ethyl 4-chloro-6-ethoxy-1,8-naphthyridine-3-carboxylate, m.p. 243-250°C.
- 10 B5: 1-(4-Chloro-6-ethoxy-7-methyl-1,8-naphthyridine-1-yl)-1-butanone, m.p. 137-139°C.
- B6: Ethyl 4-chloro-7-ethoxy-1,8-naphthyridine-3-carboxylate, m.p. 72-75°C.
- B7: Ethyl 6-bromo-4-chloro-7-methyl-1,8-naphthyridine-3-carboxylate, m.p. 222-224°C.
- 15 B8: Methyl 5-chloro-1,8-naphthyridine-2-carboxylate, m.p. 128-133°C.
- B9: Ethyl 4-chloro-7-methyl-6-propoxy-1,8-naphthyridine-3-carboxylate, m.p. 100-106°C.
- 20 B10: Ethyl 4-chloro-6-methoxy-7-methyl-1,8-naphthyridine-3-carboxylate, m.p. 130°C.
- B11: 6-Bromo-5-chloro-3-ethoxy-2-methyl-1,8-naphthyridine, m.p. 194-195°C.
- B12: 5-Chloro-2,6-dimethyl-3-ethoxy-1,8-naphthyridine, m.p. 140-144°C.

25 Example B13

In a similar manner to Example B1, a mixture of 6-bromo-7-methyl-1,8-naphthyridin-4-ol (3.7 g) and phosphorus oxychloride (25 ml) was stirred at 95°C for 1 hour to give 3-bromo-5-chloro-2-methyl-1,8-naphthyridine, m.p. 160-164°C.

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Example B14

6-Ethoxy-4-hydroxy-7-methyl-1,8-naphthyridine-3-carboxylic acid (8.7 g) was added with stirring to phosphorus oxychloride (75 ml) at ambient temperature. The mixture was heated at 60°C (internal temperature) for 45 minutes and then cooled to 10°C. The mixture was added dropwise to aqueous ammonia solution (specific gravity 0.88) at 10°C over 4 hours. The mixture was filtered and the solid obtained was washed with absolute ethanol (7 x 100 ml). The combined washings were evaporated under reduced pressure to give 4-chloro-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxamide, which was used without further purification.

Example B15

6-Ethoxy-2,7-dimethyl-1,8-naphthyridin-4-ol (2.77 g) was added to phosphorus oxychloride (25 ml) at ambient temperature. The mixture was then heated at 95°C for 1 hour. The mixture was worked up as described in example B1 to give 5-chloro-3-ethoxy-2,7-dimethyl-1,8-naphthyridine, m.p. 144-7°C.

Example C1

N,N-Diethyl-2-(4-nitrophenoxy)ethylamine (4.0 g) (prepared by the method described in Helv. Chim. Acta. 1960, 43, 1971) was dissolved in IMS (70 ml), water (10 ml) and concentrated hydrochloric acid (2 ml). The mixture was boiled under reflux and then reduced iron powder (4.6 g) was carefully added in portions. The mixture was boiled under reflux for 7 hours then hot filtered. The filtrate was basified with 5M sodium hydroxide solution and then evaporated under reduced pressure. The residue was partitioned between water and ether. The organic layer was separated, dried and

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evaporated to give 4-[2-(N,N-diethylamino)-ethoxy]aniline as an oil.

Example C2

4-(1-Adamantyloxy)aniline was prepared as described  
5 in J. Med. Chem. 1979, 22, 69.

Example C3

A solution of 3-(4-nitrophenoxy)propane-1,2-diol  
(5.0 g) in absolute ethanol (250 ml) was hydrogenated at  
atmospheric pressure in the presence of 10% palladium on  
10 charcoal (150 mg). After the uptake of hydrogen had  
ceased, the catalyst was removed by filtration. The  
filtrate was evaporated under reduced pressure to give  
3-(4-aminophenoxy)propane-1,2-diol as a solid which was  
used without further purification.

15 Example C4

2-(4-Aminophenoxy)ethanol was prepared, using the  
method described in Example C3, by the reduction of 2-  
(4-nitrophenoxy)ethanol which was prepared by heating a  
mixture of 4-chloronitrobenzene, ethylene glycol and  
20 sodium carbonate in a sealed vessel (Beil. 6, II, 222).

Example C5

4-Amino-2,6-dimethylphenol hydrochloride was  
prepared by reduction of 2,6-dimethyl-4-nitrophenol  
using the method described in Example C1. The free base  
25 initially obtained was dissolved in dichloromethane and  
concentrated hydrochloric acid was added to this  
solution to obtain the product.

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Preparation of Compounds of Formula IExample 1

A mixture of ethyl 4-chloro-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxylate (3.5 g) and 4-methoxyaniline (1.5 g) in ethanol (50 ml) was boiled under reflux for 1.5 hours. The reaction mixture was concentrated to half the volume, cooled and ether added. The solid was collected by filtration and dried to give ethyl 4-(4-methoxyanilino)-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxylate hydrochloride m.p. 260-262°C (with decomposition).

Active (1/2) 10 mg/kg; Active (4/5) 30 mg/kg.

Example 2-33

In a similar manner to Example 1, compounds of formula I were prepared by reacting a compound of formula III with a compound of formula IV, in which OR<sub>6</sub> is located in the 4-position, as summarised in Table 2.



TABLE 2

Ex	III	Substituents on IV		R <sub>6</sub>	Weight of IV (g)	EtOH (ml)	Reflux Time (Hours)	Notes
		R <sub>7</sub>	R <sub>8</sub>					
2	B2	2.0	H	CH <sub>3</sub>	0.84	25	5	1
3	B3	2.7	H	CH <sub>3</sub>	1.1	50	2	2
4	B4	1.8	H	CH <sub>3</sub>	0.79	50	1	2
5	B5	3.3	H	CH <sub>3</sub>	1.4	95	18	3
6	B6	6.9	H	CH <sub>3</sub>	3.0	100	17	4
7	B7	1.7	H	CH <sub>3</sub>	0.64	25	1.5	2
8	B13	1.5	H	CH <sub>3</sub>	0.80	25	24	5
9	B1	2.0	H	(CH <sub>2</sub> ) <sub>2</sub> OH	0.92	45	18	6
10	B1	2.0	2-CH <sub>3</sub>	CH <sub>3</sub>	0.93	40	6.5	7
11	B2	2.0	2-CH <sub>3</sub>	CH <sub>3</sub>	1.2	35	6.75	7
12	B2	2.0	H	CH <sub>2</sub> CH <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1.8	55	18	8
13	B2	1.9	3-CH <sub>3</sub>	H	1.6	30	3	5
14	B2	2.0	H	1-Adamantyl	2.2	45	18	3
15	B2	2.0	H	Ph	1.75	40	20	5
16	B1	2.0	H	C <sub>2</sub> H <sub>5</sub>	0.93	45	18	3
17	B1	2.0	H	CF <sub>3</sub>	1.3	45	18	3
18	B1	2.0	H	CH <sub>2</sub> Ph	1.35	45	18	3

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		Substituents on IV									
Ex	III	Weight of III (g)	R <sub>7</sub>	R <sub>8</sub>	R <sub>6</sub>	Weight of IV (g)	EtoH (ml)	Reflux Time (Hours)	Notes		
19	B8	14.0	H	H	CH <sub>3</sub>	7.74	200	18			
20	B1	2.2	H	H	CH <sub>2</sub> CH(OH)CH <sub>2</sub> OH	1.36	50	18	3		
21	B1	0.78	3-CH <sub>3</sub>	H	H	0.33	35	5	3		
22	B1	2.0	H	H	(CH <sub>2</sub> ) <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1.30	50	18	3		
23	B1	2.9	3-CH <sub>3</sub>	5-CH <sub>3</sub>	CH <sub>3</sub>	1.36	40	2	9		
24	B2	2.0	3-Cl	5-Cl	H	1.60	50	18	3		
25	B14	6.7	H	H	CH <sub>3</sub>	3.10	110	2	9		
26	B9	1.7	H	H	CH <sub>3</sub>	0.70	140	2	4		
27	B10	2.34	H	H	CH <sub>3</sub>	1.10	40	2	4		
28	B11	2.8	H	H	CH <sub>3</sub>	1.14	125	3.3	5		
29	B1	3.0	H	3-CO <sub>2</sub> H	H	1.64	100	2.5	5		
30	B15	1.97	H	H	CH <sub>3</sub>	1.10	140	2.5	2		
31	B12	3.45	H	H	CH <sub>3</sub>	1.80	30	18	5		
32	B1	2.0	3-OCH <sub>3</sub>	5-OCH <sub>3</sub>	CH <sub>3</sub>	1.25	35	4.5	7		
33	B2	1.08	H	H	CH <sub>2</sub> CH(OH)CH <sub>2</sub> OH	0.90	30	18	3		

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Notes to Table 2

- (1) No ether added after concentration of the reaction mixture.
- 5 (2) Reaction mixture not concentrated but diluted with ethyl acetate to induce crystallisation.
- (3) Reaction mixture not concentrated but diluted with ether to induce crystallisation.
- 10 (4) The reaction mixture was cooled and basified with triethylamine. This mixture was partitioned between water and ethyl acetate. The organic layer was separated and purified by flash chromatography on silica using ethyl acetate as the mobile phase. The main fractions were combined and evaporated. This residue was dissolved in IMS and hydrogen chloride gas passed through the solution. The solution was evaporated to dryness under reduced pressure. The residue was triturated with ether then filtered to give the product.
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- 20 (5) The hydrochloride of the compound of formula IV was used. The reaction mixture was cooled and filtered to give the product.
- (6) Ether was added to the cooled reaction mixture whereupon an oil separated out. The supernatant solvent was decanted from the oil and triturated with more ether to give a solid product which was collected by filtration.
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- (7) The reaction mixture was evaporated to dryness under reduced pressure and the residue triturated with ether to give a solid. The solid was collected by filtration, dissolved in IMS and purified by column chromatography using activated
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magnesium silicate as the stationary phase and IMS as the mobile phase.

(8) A few drops of concentrated hydrochloric acid were added to the initial reaction mixture. After heating, the mixture was cooled and filtered. The residue was recrystallised from IMS/ether.

(9) As in note 7 but dichloromethane was used as the mobile phase.

The compounds obtained in Examples 2-33 were as follows:-

Example 2: 3-Ethoxy-5-(4-methoxyanilino)-2-methyl-1,8-naphthyridine hydrochloride, m.p. 246-251°C.  
Active (2/2) at 30 mg/kg.

Example 3: Ethyl 4-(4-methoxyanilino)-7-trifluoromethyl-1,8-naphthyridine-3-carboxylate hemihydrochloride, m.p. 214-217°C.  
Active (1/1) at 30 mg/kg.

Example 4: Ethyl 6-ethoxy-4-(4-methoxyanilino)-1,8-naphthyridine-3-carboxylate hydrochloride, m.p. 213-215°C.  
Active (1/1) at 30 mg/kg.

Example 5: 3-Butyryl-6-ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine hydrochloride, m.p. 236-240°C.  
Borderline active (1/1) at 30 mg/kg.

Example 6: Ethyl 7-ethoxy-4-(4-methoxyanilino)-1,8-naphthyridine-3-carboxylate hydrochloride, m.p. 156-160°C.  
Active (3/3) at 30 mg/kg.

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Example 7: Ethyl 6-bromo-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylate hydrochloride, m.p. 182-185°C (with decomposition).

Active (1/2) at 30 mg/kg. Borderline active (1/2) at 5 30 mg/kg.

Example 8: 3-Bromo-5-(4-methoxyanilino)-2-methyl-1,8-naphthyridine, m.p. 164-167°C.

Borderline active (1/1) at 30 mg/kg.

Example 9: Ethyl 6-ethoxy-4-[4-(2-hydroxyethoxy)-anilino]-7-methyl-1,8-naphthyridine-3-carboxylate hydrochloride, m.p. 190-193°C.

Active (2/2) at 30 mg/kg.

Example 10: Ethyl 6-ethoxy-4-(4-methoxy-2-methylanilino)-7-methyl-1,8-naphthyridine-3-carboxylate hemihydrochloride, m.p. 145-147°C.

Active (1/1) at 30 mg/kg.

Example 11: 3-Ethoxy-5-(4-methoxy-2-methylanilino)-2-methyl-1,8-naphthyridine sesquihydrochloride, m.p. 130°C (with decomposition).

Active (1/1) at 30 mg/kg.

Example 12: 4-[4-(2-Diethylaminoethoxy)anilino]-6-ethoxy-7-methyl-1,8-naphthyridine sesquihydrochloride hydrate, m.p. 154-158°C.

Borderline active (1/1) at 30 mg/kg.

Example 13: 4-(6-Ethoxy-7-methyl-1,8-naphthyridin-4-ylamino)-2,6-xyleneol hydrochloride, m.p. 306-308°C (with decomposition).

Active (2/2) at 30 mg/kg.

Example 14: 5-[4-(1-Adamantyloxy)anilino]-3-ethoxy-2-methyl-1,8-naphthyridine hydrochloride, m.p. 248-252°C.

Active (1/2) at 30 mg/kg.

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Example 15: 3-Ethoxy-2-methyl-5-(4-phenoxyanilino)-1,8-naphthyridine hydrochloride, m.p. 268-270°C (with decomposition).

A (1/2) 10 mg/kg, I (2/3) 30 mg/kg.

5 Example 16: Ethyl 6-ethoxy-4-(4-ethoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylate hydrochloride, m.p. 213-215°C.

Example 17: Ethyl 6-ethoxy-7-methyl-4-(4-trifluoromethoxyanilino)-1,8-naphthyridine-3-carboxylate  
10 hydrochloride, m.p. 245-250°C.

Example 18: Ethyl 4-(4-benzyloxyanilino)-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxylate hydrochloride, m.p. 213-215°C.

Example 19: Methyl 5-(4-methoxyanilino)-1,8-naphthyridine-2-carboxylate, m.p. 228-229°C.  
15

Example 20: Ethyl 4-[4-(2,3-dihydroxypropoxy)anilino]-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxylate hydrochloride, m.p. 192-196°C.

Borderline active (1/1) at 30 mg/kg.

20 Example 21: Ethyl 6-ethoxy-4-(4-hydroxy-3-methylanilino)-7-methyl-1,8-naphthyridine-3-carboxylate hydrochloride, m.p. 210-215°C.

Example 22: Ethyl 4-[4-(2-diethylaminoethoxy)anilino]-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxylate  
25 sesquihydrochloride, m.p. 135-140°C.

Active (1/1) at 30 mg/kg.

Example 23: Ethyl 6-ethoxy-4-(4-methoxy-3,5-dimethylanilino)-7-methyl-1,8-naphthyridine-3-carboxylate, m.p. 166-168°C.

30 Active (1/1) at 30 mg/kg.

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Example 24: 2,6-Dichloro-4-(6-ethoxy-7-methyl-1,8-naphthyridin-4-ylamino)phenol sesquihydrochloride dihydrate, m.p. 181-184°C.

Example 25: 6-Ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxamide, m.p. 243-245°C.

Example 26: Ethyl 4-(4-methoxyanilino)-7-methyl-6-propoxy-1,8-naphthyridine-3-carboxylate hydrochloride, m.p. 263-266°C.

Example 27: Ethyl 6-methoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylate hemihydrochloride hydrate, m.p. 155-159°C.

Example 28: 6-Bromo-3-ethoxy-5-(4-methoxyanilino)-2-methyl-1,8-naphthyridine hemihydrochloride hemihydrate, m.p. 134-137°C (after recrystallisation from ethanol).

Example 29: 5-(6-Ethoxy-3-ethoxycarbonyl-7-methyl-1,8-naphthyridin-4-ylamino)salicylic acid hydrochloride hemihydrate, m.p. 242-246°C.

Example 30: 3-Ethoxy-5-(4-methoxyanilino)-2,7-dimethyl-1,8-naphthyridine hydrochloride, m.p. 254-256°C.

Example 31: 3-Ethoxy-5-(4-methoxyanilino)-2,6-dimethyl-1,8-naphthyridine hemihydrochloride hemihydrate, m.p. 135-140°C.

Example 32: Ethyl 6-ethoxy-7-methyl-4-(3,4,5-trimethoxyanilino)-1,8-naphthyridine-3-carboxylate hemihydrochloride hydrate, m.p. 162-164°C.  
Borderline Active (1/1) at 30 mg/kg.

Example 33: 3-[4-(6-Ethoxy-7-methyl-1,8-naphthyridin-4-ylamino)phenoxy]propane-1,2-diol hydrochloride, m.p. 229-233°C.

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Example 34

In a similar manner to Example 1, a mixture of 5-chloro-3-ethoxy-2-methyl-1,8-naphthyridine (2.0 g) and 2-methoxyaniline (1.05 g) in IMS (30 ml) was boiled  
5 under reflux for 6 hours then cooled and filtered to give 3-ethoxy-5-(2-methoxyanilino)-2-methyl-1,8-naphthyridine hydrochloride, m.p. 250-252°C (with decomposition).

Active (1/1) at 30 mg/kg.

10 Example 35

In a similar manner to Example 1, a mixture of ethyl 4-chloro-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxylate (1.93 g) and 4-phenoxyaniline (1.33 g) in  
15 IMS (40 ml) was boiled under reflux for 2 hours to give ethyl 6-ethoxy-7-methyl-4-(4-phenoxyanilino)-1,8-naphthyridine-3-carboxylate hydrochloride, m.p. 213-215°C.

Active (1/2) at 30 mg/kg.

Example 36

20 In a similar manner to Example 1, a mixture 5-chloro-3-ethoxy-2-methyl-1,8-naphthyridine (2.3 g), 4-aminophenol (1.13 g) and ethanol (25 ml) was boiled under reflux for 1 hour to give 4-(6-ethoxy-7-methyl)-1,8-naphthyridin-4-ylamino)phenol hydrochloride, m.p.  
25 275-280°C.

Active (1/2) at 30 mg/kg.

Example 37

In a similar manner to Example 1, a mixture of ethyl 4-chloro-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxylate (2.43 g) and 4-methoxy-N-methylaniline  
30 (1.13 g) in IMS (25 ml) was boiled under reflux for 4



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hours then concentrated and ether (10 ml) added at 0°C. A small amount of solid was removed by filtration. The filtrate was basified with triethylamine and the mixture separated by flash chromatography on silica using ethyl acetate as the mobile phase. The residue obtained was triturated with petroleum ether b.p. 40-60°C to give ethyl 6-ethoxy-4-(4-methoxy-N-methylanilino)-7-methyl-1,8-naphthyridine-3-carboxylate, m.p. 129-132°C.

#### Example 38

10        Lithium triethylborohydride (a 1M solution in THF, 47 ml) was added to a solution of ethyl 6-ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylate (4.5 g) in THF (150 ml) with stirring under nitrogen at 0-10°C. The mixture was allowed to warm up to ambient  
15        temperature and stirred at this temperature for 18 hours. Further lithium triethylborohydride solution (15 ml) was added and the solution stirred at ambient temperature for 4 hours. The reaction mixture was cooled to 5°C and then 5M hydrochloric acid (5 ml) was  
20        added carefully followed by water (50 ml). The organic layer was separated and the aqueous layer extracted with ether. The aqueous layer was basified with 5M sodium hydroxide solution and extracted into ethyl acetate. The residue, obtained from the ethyl acetate extracts,  
25        was purified by flash chromatography on silica, using dichloromethane/IMS (15/1) as the mobile phase, to give 6-ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridin-3-ylmethanol, m.p. 193-197°C.

#### Example 39

30        A mixture of 3-ethoxy-5-(4-methoxyanilino)-2-methyl-1,8-naphthyridine hydrochloride (5.0 g), glyoxylic acid monohydrate (2.2 g) and glacial acetic acid (50 ml) were stirred and treated dropwise with trifluoroacetic acid (12.5 ml). The mixture was stirred

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and heated at 95°C for 22 hours and cooled to ambient temperature. The mixture was filtered and the solid obtained was stirred in sodium bicarbonate solution (100 ml) for 15 minutes. The mixture was filtered.

5 The solid obtained was stirred in water (100 ml) and acidified with concentrated hydrochloric acid to pH 1. After stirring for an hour the mixture was filtered to give a solid. The filtrate was evaporated to dryness and the residue triturated with water and filtered. The

10 crops of solid were combined, dissolved in dichloromethane/methanol, dried, filtered and evaporated. The residue was triturated with hot ethyl acetate and hot filtered. The solid obtained was combined with the solid obtained from the acidic mixture

15 above, triturated with hot ethyl acetate and hot filtered. The solid obtained was purified by flash column chromatography on silica using a mixture of ethyl acetate:dichloromethane:methanol, 5:5:1 and then 1:1:1 to give a solid. The solid was triturated with hot

20 ethyl acetate and hot filtered to give 3-[3-ethoxy-5-(4-methoxyanilino)-1,8-naphthyridin-2-yl]acrylic acid hydrochloride dihydrate, m.p. 230-235°C (with decomposition).

#### Example 40

25 A mixture of ethyl 6-ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylate hydrochloride (4.76 g), glyoxylic acid (1.73 g) and glacial acetic acid (50 ml) was boiled under reflux for 24 hours. The mixture was cooled and a solid was collected by

30 filtration. The filtrate was acidified with concentrated hydrochloric acid and filtered to give a second crop of solid. The two crops of solid were combined, stirred in water and the mixture basified with sodium bicarbonate. The pH of the mixture was adjusted

35 to pH 6 with concentrated hydrochloric acid and the mixture was extracted with ethyl acetate and then with

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dichloromethane. The combined organic extracts were washed with water, dried and evaporated. The residue was triturated with ethyl acetate and then filtered to give 3-[3-ethoxy-6-ethoxycarbonyl-5-(4-methoxyanilino)-  
5 1,8-naphthyridin-2-yl]acrylic acid hemihydrochloride, m.p. 259-261°C.

#### Example 41

A mixture of 3-[3-ethoxy-6-ethoxycarbonyl-5-(4-methoxyanilino)-1,8-naphthyridin-2-yl]acrylic acid  
10 (2.3 g), 10% palladium on charcoal (0.5 g), IMS (250 ml) and concentrated hydrochloric acid (0.4 ml) was shaken under an atmosphere of hydrogen until uptake of hydrogen ceased. The catalyst was removed by filtration and the filtrate was evaporated. The residue was triturated  
15 with hot ethyl acetate and hot filtered to give 3-[3-ethoxy-6-ethoxycarbonyl-5-(4-methoxyanilino)-1,8-naphthyridin-2-yl]propionic acid hydrochloride, m.p. 213-216°C

#### Example 42

20 A mixture ethyl 6-ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylate (6.38 g), water (40 ml), sodium hydroxide solution (120 ml, 0.6M) was boiled and stirred under reflux for 2 hours and then allowed to cool. The mixture was acidified with 5M  
25 hydrochloric acid (100 ml) and filtered. The filtrate was extracted with dichloromethane to give a residue which was washed with 5M hydrochloric acid and filtered to give 6-ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylic acid, m.p. 259-263°C.

#### 30 Example 43

A mixture of ethyl 7-ethoxy-4-(4-methoxyanilino)-1,8-naphthyridine-3-carboxylate hydrochloride (2.6 g)

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and 5M sodium hydroxide solution (60 ml) was heated on a steam bath for 4 hours. The mixture was cooled and filtered. The residue was dissolved in IMS and hydrogen chloride gas bubbled through this solution. Ether was added to induce crystallisation and the mixture was filtered to give ethyl 4-[4-methoxyanilino]-7-oxo-7,8-dihydro-1,8-naphthyridine-3-carboxylate 0.3 hydrochloride hemihydrate, m.p. 243-246°C.

#### Example 44

10 A mixture of methyl 5-(4-methoxyanilino)-1,8-naphthyridine-2-carboxylate (1.0 g) and dry THF (100 ml) was stirred at 0°C while lithium triethylborohydride (a 1M solution in THF, 6.5 ml) was added over 10 minutes. After stirring at 0°C for 1 hour  
15 further lithium triethylborohydride solution (3 ml) was added. The mixture was stirred for a further 1.5 hours at 0°C. Water (100 ml) was added cautiously and the mixture was extracted with ethyl acetate. The ethyl acetate extract was extracted with 0.5M hydrochloric  
20 acid. The acid extract was washed with ethyl acetate, basified with sodium bicarbonate and extracted with dichloromethane:methanol (3:1) (2 x 200 ml) to give a residue which was triturated with methanol and filtered. The solid obtained was triturated with ethyl acetate and  
25 filtered to give 5-(4-methoxyanilino)-1,8-naphthyridine-2-ylmethanol, m.p. 275-281°C.

#### Example 45

A solution of 3-butyryl-6-ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine (8.0 g) in  
30 absolute ethanol (200 ml) was added dropwise at 0°C over 1 hour to a solution of sodium borohydride (2.4 g) in absolute ethanol (200 ml). The mixture was allowed to warm up to ambient temperature and stirred at this temperature for 18 hours. Glacial acetic acid was

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added carefully to destroy excess borohydride and the resulting mixture was concentrated under reduced pressure. The residue was dissolved in water (200 ml) and extracted with dichloromethane to give a residue  
5 which was dissolved in IMS and saturated with hydrogen chloride gas. Ether was added to induce crystallisation. The mixture was filtered to give 1-[6-ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridin-3-yl]butan-1-ol, m.p. 120-124°C.

10 Example 46

A mixture of ethyl 4-(4-methoxyanilino)-6-ethoxy-7-methyl-1,8-naphthyridine-3-carboxylate (2.9 g) in dichloromethane (45 ml) was added rapidly to a suspension of powdered anhydrous aluminium chloride  
15 (12.8 g) in dichloromethane (115 ml) with stirring. The mixture was stirred for 24 hours at ambient temperature and then poured into ice/water. The mixture was stirred for 30 minutes then filtered. The residue was basified and partitioned between dichloromethane and water. The  
20 aqueous layer was evaporated to dryness. The residue was dissolved in propan-2-ol (150 ml) and then purified by column chromatography to give 6-hydroxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylic acid hemihydrate, m.p. 267-268°C (with decomposition).

25 Example 47

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing  
30 mg active compound.

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Example 48

Tablets are prepared from the following ingredients.

		<u>Parts by Weight</u>
5	Active compound	10
	Lactose	190
	Maize starch	22
	Polyvinylpyrrolidone	10
	Magnesium stearate	3
10	The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinylpyrrolidone in ethanol. The dry granulate is blended with magnesium stearate and the rest of the starch. The mixture is	
15	then compressed in a tableting machine to give tablets containing 10 mg of active compound.	

Example 49

Tablets are prepared by the method of the previous Example. The tablets are enteric coated in a  
20 conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

Example 50

In the preparation of suppositories, 100 parts by  
25 weight of active compound is incorporated in 1300 parts by weight of semi-synthetic glycerides as the suppository base and the mixture formed into suppositories each containing 100 mg of active ingredient.

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Example 51

In the preparation of capsules, 50 parts by weight of active compound, 300 parts by weight of lactose and 3 parts by weight of magnesium stearate are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing 50 mg of active ingredient.

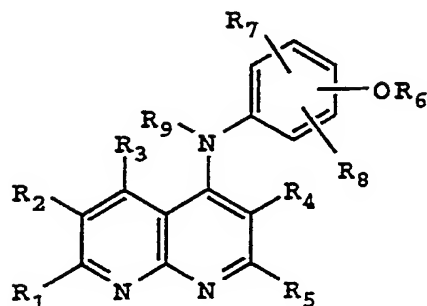
Example 52

The active compound is incorporated into the base by thorough homogenization until the drug is evenly distributed. The ointment is packed into 10 g amber jars with screw-capped lined lids.

Active compound	0.1 g
White soft paraffin to	10 g

CLAIMS

## 1. Compounds of formula I



I

and pharmaceutically acceptable salts thereof, in which  
 R<sub>1</sub> represents hydrogen, a C<sub>1-6</sub> alkyl group, hydroxy, a  
 5 carboxy C<sub>2-4</sub> alkenyl group, a C<sub>2-6</sub> alkoxy carbonyl C<sub>2-4</sub>  
 alkenyl group, a hydroxy C<sub>1-6</sub> alkyl group, a carboxy  
 C<sub>1-4</sub> alkyl group, a C<sub>2-6</sub> alkoxy carbonyl C<sub>1-4</sub> alkyl  
 group, a C<sub>1-6</sub> alkoxy group, a halogenated C<sub>1-6</sub> alkyl  
 group, a carboxy group, a C<sub>2-6</sub> alkoxy carbonyl group or a  
 10 C<sub>1-6</sub> alkanoylamino group;

R<sub>2</sub> represents hydrogen, halo, a C<sub>1-6</sub> alkoxy group,  
 hydroxy, a C<sub>1-6</sub> alkanoyloxy group, or a phenoxy group  
 (which may be optionally substituted by a C<sub>1-4</sub> alkyl  
 group, halo or a C<sub>1-4</sub> alkoxy group);

15 R<sub>3</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group;

R<sub>4</sub> represents hydrogen, halo, a C<sub>2-7</sub> alkoxy carbonyl  
 group, a benzyloxy carbonyl group (which may be  
 optionally substituted by a C<sub>1-4</sub> alkyl group, halo or a  
 C<sub>1-4</sub> alkoxy group), a C<sub>1-6</sub> alkanoyl group, a benzoyl  
 20 group (which may be optionally substituted by a C<sub>1-4</sub>  
 alkyl group, halo or a C<sub>1-4</sub> alkoxy group), carbamoyl, a  
 C<sub>1-6</sub> alkyl group, a carboxy group, a C<sub>1-6</sub> hydroxyalkyl  
 group or a C<sub>1-6</sub> alkylthio group;



R<sub>5</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group;

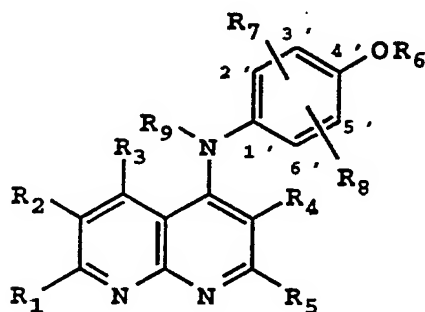
R<sub>6</sub> represents hydrogen, a C<sub>1-6</sub> alkyl group [optionally substituted by one or more of the following: hydroxy, halo or an amino group of formula-NR<sub>12</sub>R<sub>13</sub> (in which R<sub>12</sub> and R<sub>13</sub> independently represent hydrogen or a C<sub>1-4</sub> alkyl group or R<sub>12</sub> and R<sub>13</sub> together with the nitrogen atom to which they are attached represent a pyrrolidine ring, a morpholine ring or a piperidine ring)], a C<sub>3-12</sub> alicyclic hydrocarbon group, a phenyl group (which may be optionally substituted by a C<sub>1-4</sub> alkyl group, halo or a C<sub>1-4</sub> alkoxy group), a C<sub>3-6</sub> cycloalkyl C<sub>1-4</sub> alkyl group or a benzyl group (which may be optionally substituted by a C<sub>1-4</sub> alkyl group, halo or a C<sub>1-4</sub> alkoxy group);

R<sub>7</sub> represents hydrogen, halo, trifluoromethyl, trifluoromethoxy, a C<sub>1-6</sub> alkyl group, a carboxy group, or a C<sub>1-6</sub> alkoxy group;

R<sub>8</sub> represents hydrogen, halo, trifluoromethyl, trifluoromethoxy, a C<sub>1-6</sub> alkyl group or a C<sub>1-6</sub> alkoxy group; and

R<sub>9</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group.

2. Compounds according to claim 1 represented by formula II



II

and pharmaceutically acceptable salts thereof in which

R<sub>1</sub> represents hydrogen, a C<sub>1-4</sub> alkyl group, hydroxy, a carboxy C<sub>2-4</sub> alkenyl group, a C<sub>2-6</sub> alkoxy carbonyl vinyl group, an ω-hydroxy C<sub>1-4</sub> alkyl group, a carboxy C<sub>1-4</sub> alkyl group, a C<sub>2-6</sub> alkoxy carbonyl C<sub>1-4</sub> alkyl group, a  
5 C<sub>1-6</sub> alkoxy group, or a polyhalogenated C<sub>1-4</sub> alkyl group;

R<sub>2</sub> represents hydrogen, halo, C<sub>1-6</sub> alkoxy group or hydroxy;

R<sub>3</sub> represents hydrogen;

10 R<sub>4</sub> represents hydrogen, halo, a C<sub>2-5</sub> alkoxy carbonyl group, benzyloxy carbonyl, a C<sub>2-6</sub> alkanoyl group carbamoyl, a C<sub>1-4</sub> alkyl group, carboxy or an α-hydroxy C<sub>1-6</sub> alkyl group;

R<sub>5</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group;

15 R<sub>6</sub> represents hydrogen, a C<sub>1-6</sub> alkyl group [optionally substituted by one or more of the following hydroxy, halo or an amino group of formula NR<sub>12</sub>R<sub>13</sub> in which R<sub>12</sub> and R<sub>13</sub> independently represent hydrogen or a C<sub>1-4</sub> alkyl group], a C<sub>3-12</sub> alicyclic hydrocarbon group, phenyl or  
20 benzyl;

R<sub>7</sub> represents hydrogen, halo, trifluoromethyl, a C<sub>1-4</sub> alkyl group or a carboxy group;

R<sub>8</sub> represents hydrogen, halo, trifluoromethyl, a C<sub>1-4</sub> alkyl group or a C<sub>1-4</sub> alkoxy group; and

25 R<sub>9</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group.

3. Compounds according to claim 2 in which R<sub>1</sub> represents hydrogen, methyl, ethoxy, trifluoromethyl, hydroxy, 2-carboxyvinyl, 2-carboxyethyl or hydroxymethyl.

4. Compounds according to either one of claims 2 or 3 in which  $R_2$  represents hydrogen, methoxy, ethoxy, propoxy or bromo.
5. Compounds according to any one of claims 2 to 4 in which  $R_3$  represents hydrogen.
6. Compounds according to any one of claims 2 to 5 in which  $R_4$  represents hydrogen, bromo, ethoxycarbonyl, 1-butyryl, carboxy, carbamoyl, hydroxymethyl or 1-hydroxybutyl.
- 10 7. Compounds according to any one of claims 2 to 6 in which  $R_5$  represents hydrogen or methyl.
8. Compounds according to any one of claims 2 to 7 in which  $R_6$  represents hydrogen, methyl, ethyl, 1-adamantyl, phenyl, 2-(diethylamino)ethyl, 2-hydroxyethyl, 2,3-dihydroxypropyl, trifluoromethyl or benzyl.
- 15 9. Compounds according to any one of claims 2 to 8 in which  $R_7$  represents hydrogen, 2'-methyl, 3'-methyl, 3'-methoxy, 3'-chloro or 3'-carboxy.
- 20 10. Compounds according to any one of claims 2 to 9 in which  $R_8$  represents hydrogen, 5'-methyl, 5'-methoxy or 5'-chloro.
11. Compounds according to any one of claims 2 to 10 in which  $R_9$  represents hydrogen or methyl.
- 25 12. Compounds according to claim 2 in which  $R_1$  represents hydrogen, a  $C_{1-4}$  alkyl group or 2-carboxyvinyl;  $R_2$  represents a  $C_{2-4}$  alkoxy group;  $R_3$  represents hydrogen;  $R_4$  represents a  $C_{3-4}$  alkoxycarbonyl group;  $R_5$  represents hydrogen;  $R_6$  represents a  $C_{1-4}$  alkyl group, phenyl, benzyl, trifluoromethyl, 2-
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hydroxyethyl, 2-(diethylamino)ethyl, 2,3-dihydroxypropyl; R<sub>7</sub> represents hydrogen or 2'-methyl and R<sub>8</sub> and R<sub>9</sub> represent hydrogen.

13. Compounds according to claim 2 in which R<sub>1</sub> represents hydrogen, hydroxy, ethoxy or trifluoromethyl; R<sub>2</sub> represents hydrogen; R<sub>3</sub> represents hydrogen; R<sub>4</sub> represents a C<sub>3-4</sub> alkoxy carbonyl group; R<sub>5</sub> represents hydrogen; R<sub>6</sub> represents a C<sub>1-4</sub> alkyl group (which may be optionally substituted by one or more of the following: hydroxy, halo or an amino group of formula -NR<sub>12</sub>R<sub>13</sub> in which R<sub>12</sub> and R<sub>13</sub> independently represents hydrogen or a C<sub>1-4</sub> alkyl group); and R<sub>7</sub>, R<sub>8</sub> and R<sub>9</sub> each represent hydrogen.

14. Compounds according to claim 2 in which R<sub>1</sub> represents a C<sub>1-4</sub> alkyl group; R<sub>2</sub> represents a C<sub>2-4</sub> alkoxy group; R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> represent hydrogen; R<sub>7</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group; R<sub>8</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group; and R<sub>9</sub> represents hydrogen.

15. Compounds of formula I as claimed in claim 1 selected from:

Ethyl 6-ethoxy-4-(4-methoxyanilino)-7-methyl-1,8-naphthyridine-3-carboxylate,

3-Ethoxy-5-(4-methoxyanilino)-2-methyl-1,8-naphthyridine,

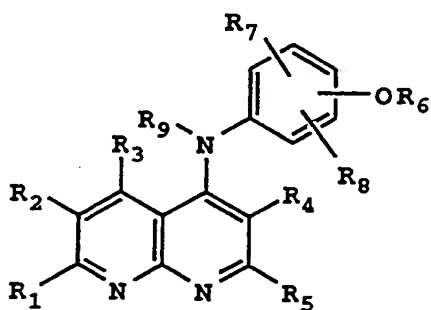
Ethyl 7-ethoxy-4-(4-methoxyanilino)-1,8-naphthyridine-3-carboxylate,

Ethyl 6-ethoxy-4-[4-(2-hydroxyethoxy)anilino]-7-methyl-1,8-naphthyridine-3-carboxylate and

4-(6-Ethoxy-7-methyl-1,8-naphthyridin-4-ylamino)-2,6-xyleneol;

and pharmaceutically acceptable salts thereof.

16. A pharmaceutical composition containing a therapeutically effective amount of a compound of formula I as claimed in any one of claims 1-15 together with a pharmaceutically acceptable diluent or carrier.
17. The use of a compound of formula I as claimed in any one of claims 1 to 15 as a medicament.
18. The use of compounds of formula I as claimed in any one of claims 1 to 15 in the treatment of rheumatic diseases.
19. The use of a compound of formula I as claimed in any one of claims 1 to 15 in the manufacture of a medicament for use in the treatment of rheumatic diseases.
20. A method of treating rheumatic diseases, comprising the administration of a therapeutically effective amount of a compound of formula I as claimed in any one of claims 1 to 15 to a mammal in need thereof.
21. A process to prepare a compound of formula I



- and pharmaceutically acceptable salts thereof
- 20 in which

$R_1$  represents hydrogen, a  $C_{1-6}$  alkyl group, hydroxy, a carboxy  $C_{2-4}$  alkenyl group, a  $C_{2-6}$  alkoxy carbonyl  $C_{2-4}$  alkenyl group, a hydroxy  $C_{1-6}$  alkyl group, a carboxy  $C_{1-4}$  alkyl group, a  $C_{2-6}$  alkoxy carbonyl  $C_{1-4}$  alkyl

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group, a C<sub>1-6</sub> alkoxy group, a halogenated C<sub>1-6</sub> alkyl group, a carboxy group, a C<sub>2-6</sub> alkoxy carbonyl group or a C<sub>1-6</sub> alkanoylamino group;

5 R<sub>2</sub> represents hydrogen, halo, a C<sub>1-6</sub> alkoxy group, hydroxy, a C<sub>1-6</sub> alkanoyloxy group, or a phenoxy group (which may be optionally substituted by a C<sub>1-4</sub> alkyl group, halo or a C<sub>1-4</sub> alkoxy group);

R<sub>3</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group;

10 R<sub>4</sub> represents hydrogen, halo, a C<sub>2-7</sub> alkoxy carbonyl group, a benzyloxy carbonyl group (which may be optionally substituted by a C<sub>1-4</sub> alkyl group, halo or a C<sub>1-4</sub> alkoxy group), a C<sub>1-6</sub> alkanoyl group, a benzoyl group (which may be optionally substituted by a C<sub>1-4</sub> alkyl group, halo or a C<sub>1-4</sub> alkoxy group), carbamoyl, a  
15 C<sub>1-6</sub> alkyl group, a carboxy group, a C<sub>1-6</sub> hydroxyalkyl group or a C<sub>1-6</sub> alkylthio group;

R<sub>5</sub> represents hydrogen or a C<sub>1-4</sub> alkyl group;

R<sub>6</sub> represents hydrogen, a C<sub>1-6</sub> alkyl group [optionally substituted by one or more of the following: hydroxy, halo or an amino group of formula-NR<sub>12</sub>R<sub>13</sub> (in which R<sub>12</sub> and R<sub>13</sub> independently represent hydrogen or a C<sub>1-4</sub> alkyl group or R<sub>12</sub> and R<sub>13</sub> together with the nitrogen atom to which they are attached represent a pyrrolidine ring, a morpholine ring or a piperidine ring)], a C<sub>3-12</sub>  
20 alicyclic hydrocarbon group, a phenyl group (which may be optionally substituted by a C<sub>1-4</sub> alkyl group, halo or a C<sub>1-4</sub> alkoxy group), a C<sub>3-6</sub> cycloalkyl C<sub>1-4</sub> alkyl group or a benzyl group (which may be optionally substituted by a C<sub>1-4</sub> alkyl group, halo or a C<sub>1-4</sub> alkoxy group);  
25

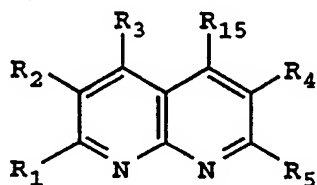
30 R<sub>7</sub> represents hydrogen, halo, trifluoromethyl, trifluoromethoxy, a C<sub>1-6</sub> alkyl group, a carboxy group, or a C<sub>1-6</sub> alkoxy group;

$R_8$  represents hydrogen, halo, trifluoromethyl, trifluoromethoxy, a  $C_{1-6}$  alkyl group or a  $C_{1-6}$  alkoxy group; and

$R_9$  represents hydrogen or a  $C_{1-4}$  alkyl group;

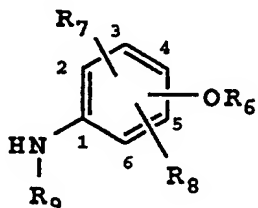
5 comprising:

a) reacting a compound of formula III



III

in which  $R_{15}$  represents a leaving group with a compound of formula IV

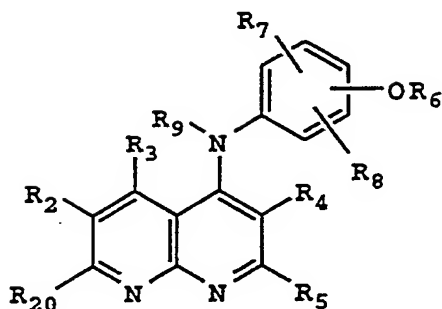


IV

or a salt thereof by heating, optionally in the presence of an inert organic liquid which is preferably a solvent for the reactants, at a temperature in the range 0-150°C, at atmospheric pressure, optionally in the presence of an acid or a base; or

b) reacting a compound of formula I in which  $R_6$  represents hydrogen with a compound of formula  $R_6L$  (XVI) in which L represents a leaving group for example halo, by heating, optionally in the presence of an inert organic liquid which is preferably a solvent for the reactants, at a temperature in the range 0-150°C, at atmospheric pressure, preferably in the presence of a base; or

c) reacting a compound of formula XVII



X V I I

in which R<sub>20</sub> represents a leaving group with an alkali metal C<sub>1-6</sub> alkoxide by heating, optionally in the presence of an inert organic liquid which is preferably  
 5 a solvent for the reactants, at a temperature in the range 50-250°C, to prepare a compound of formula I in which R<sub>1</sub> represents a C<sub>1-6</sub> alkoxy group; or

d) displacing R<sub>20</sub> from a compound of formula XVII, in which R<sub>20</sub> represents a leaving group, with a hydroxy  
 10 group, for example by reacting with an alkali metal hydroxide in the presence of an inert organic liquid or by hydrolysis using an aqueous acid or base, at a temperature in the range 0-200°C, to prepare a compound of formula I in which R<sub>1</sub> represents hydroxy; or

15 e) reducing a compound of formula I in which R<sub>1</sub> represents a carboxy C<sub>2-4</sub> alkenyl group with a reducing agent to prepare a compound of formula I in which R<sub>1</sub> represents a carboxy C<sub>2-4</sub> alkyl group; or

f) hydrolysis of a compound of formula I in which R<sub>1</sub>  
 20 represents a C<sub>1-6</sub> alkoxy group, for example using a base



e.g. sodium hydroxide, to prepare a compound of formula I in which R<sub>1</sub> represents hydroxy; or

g) reducing a compound of formula I in which R<sub>4</sub> represents a C<sub>2-7</sub> alkoxy carbonyl group or a C<sub>1-6</sub> alkanoyl group to prepare a compound of formula I in which R<sub>4</sub> represents an  $\alpha$ -hydroxy C<sub>1-6</sub> alkyl group; or

h) reacting a compound of formula I in which R<sub>2</sub> represents a C<sub>1-6</sub> alkoxy group with a de-alkylating agent to prepare a compound of formula I in which R<sub>2</sub> represents hydroxy.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 92/02901

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07D471/04; A61K31/435; //(C07D471/04,221:00,221:00)		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	C07D ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claims No. <sup>13</sup>
A	PHARMACOLOGICAL RESEARCH COMMUNICATIONS vol. 11, no. 2, 1979, LONDON, GB pages 179 - 193 R. DUANE SOFIA ET AL. 'Comparative effects of antiarthritic and other pharmacological agents in the 18-hour arthritis and carrageenan edema tests in rats' see table II, line 1; page 184, lines 22-25 and page 188, lines 1-13 -----	1,16
X	EP,A,0 410 762 (ELI LILLY) 30 January 1991 see claim 1 -----	1
<p><sup>10</sup> Special categories of cited documents :<sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
22 MARCH 1993	26. 03. 93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	ALFARO FAUS I.	

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 92/02901

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim 20 is directed to a method of treatment of (diagnostic method practised on ) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

EP 9202901  
SA 67776

**22/03/93**

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0410762	30-01-91	AU-A- 5982590	31-01-91
		JP-A- 3086881	11-04-91
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